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(54) Title: ATRIAL NATRIURETIC PEPTIDE CLEARANCE INHIBITORS

(57) Abstract

Compounds with natriuretic, diuretic and/or vasodilation activity which enhance the function of an endogenous ANP are provided. These compounds are capable of both binding to the clearance receptors for ANP and of inhibition of endopeptidase 24.11, an enzyme believed responsible for ANP clearance.

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ATRIAL NATRIURETIC PEPTIDE CLEARANCE INHIBITORS

Technical Field

The invention relates to synthetic peptides which are useful as diuretics, natriuretics, and/or vasodilators in animal subjects. More particularly, the invention concerns peptides which block specific clearance receptors for atrial natriuretic peptides and which also inhibit peptidases for which atrial natriuretic peptides are substrates.

Background Art

Atrial natriuretic peptides (ANP) are circulating hormones which are synthesized in the atrium of the heart and secreted. The hormones regulate blood pressure through their natriuretic, diuretic and vasorelaxant activities, as well as inhibition of aldosterone secretion from the adrenal gland, inhibition of renin secretion from the kidney, and functional antagonism of the renin-angiotensin system. The ANP hormones have been widely studied, and a large number of analogs have been proposed. Copending U.S. applications 138,893, filed 24 December 1987 and 237,299, filed 26 August 1988, assigned to the same assignee and incorporated herein by reference discloses a series of linear analogs of the native ANP, which native ANPs are cyclic disulfides. Cyclic analogs

are disclosed in copending application 174,739, filed 31 May 1988, assigned to the same assignee and also incorporated herein by reference. These copending applications are the latest filed in a series which includes U.S. Serial No. 168,661, filed 16 March 1988 (allowed), U.S. Serial No. 921,360 (abandoned), U.S. Serial No. 904,091 (abandoned), U.S. Serial No. 868,312 now issued as U.S. Patent No. 4,757,048, and U.S. Serial No. 795,220 (abandoned). Various analogs have also been proposed by others, and the literature relating to ANP analogs is now quite extensive.

It is known that the half life of ANPs in the blood stream is relatively short and that many of the analogs of ANP, such as those set forth in the above-referenced U.S. Serial No. 138,893, appear to act by blocking the clearance receptors for ANP, thus increasing the opportunity for the natively produced ANPs to exert their effects. Two distinct pathways have now been identified which appear to contribute to most ANP clearance. The first pathway relates to receptor mediated metabolic clearance which has sufficient affinity and capacity to account for 70-80% of total ANP clearance from the system (Maack, T., et al, Science (1987) 238:675-679, EPO Publication No. 233,143). It was further determined that an additional, nonsaturatable clearance pathway also operates if the specific receptor pathway is inhibited, Almeida, F.A., Amer J Physiol (1988) (submitted).

On the basis of additional evidence from a variety of sources, it is believed that the nonsaturatable clearance pathway may involve the activity of a peptidase, neutral endopeptidase 24.11 (EC3.4.24.11), commonly referred to as endopeptidase 24.11. U.S. 4,740,499, issued 26 April 1988, describes and claims a method of prolonging or enhancing the bioactivity of an atrial peptide using two specific inhibitors of endopeptidase 24.11, thiorphan or kelatorphan. These inhibitors are

administered simultaneously with the atrial peptide. EPO Application Publication No. 254,032, published 27 January 1988, also describes and claims the use of inhibitors of endopeptidase 24.11, or of neutral metallopeptidases in general, to treat hypertension, either alone or in association with ANP (or with an angiotensin converting enzyme inhibitor). In this disclosure, the inhibitors of the neutral metalloendopeptidase include thiorphan but further include compounds disclosed in U.S. 4,610,816, i.e., a substantial class of compounds, and compounds disclosed in EPO Application Publication No. 117,429 which also includes a substantial class. Reference is also made to compounds disclosed in U.S. Serial No. 32,153, filed 27 March 1987, U.S. Patent 4,513,009 and European Application 38,046. In addition, a large volume of literature supports the conclusion that endopeptidase 24.11 is responsible for the extracellular inactivation of ANP (Stevenson, S.L., et al, Biochem J (1987) 243:183-187; Olins, G.M., et al, Biochim Biophys Acta (1987) 901:97-100; Koehn, J.A., et al, J Biol Chem (1987) 262:11623-11627); including the observation that a metabolic fragment of ANP isolated from human plasma is identical to the primary cleavage product of ANP treated with endopeptidase 24.11 (Yandle, T., et al, Biochem Biophys Res Commun (1987) 146:832-839).

It has also been observed by others that inhibitors of endopeptidase 24.11 potentiates the biological responses of administered ANP (Fennell, S.A., et al, FASEB J (1988) 2:A936; Seymour, A.A., et al, ibid; Trapani, A.J., et al, ibid; McMartin, C., et al, ibid; Zimmerman, M.B., et al, ibid:A937).

In addition to the use of thiorphan, there has been disclosed a variety of strategies for the inhibition of endopeptidase 24.11. These strategies include the use of a metal binding substituent appropriately spaced from an aromatic moiety. Roques, B.P., et al, Nature (1980)

288:286-288; Gordon, E.M., et al, Life Sci (1983) 33(Supplement 1):113-116; Mumford, R.M., et al, Biochem Biophys Res Comm (1982) 109:1303-1309; Fournie-Zaluski, M.C., et al, J Med Chem (1983) 26:60-65; Waksman, G., et al, Biochem Biophys Res Comm (1985) 131:262-268.

Blockage of both the specific receptor and the nonsaturatable endopeptidase 24.11 based clearance mechanisms by suitable inhibitors should greatly enhance the circulating levels of ANP and prolong the activity of the endogenous hormones. Indeed, it has been shown that conscious rats treated with an ANP clearance receptor-specific ligand in combination with the endopeptidase 24.11 inhibitor thiorphan results in greater diuresis and natriuresis than blockade of either pathway alone (Koepke, J., et al, FASEB Jour (1988) 2:A527. However, administration of inhibitors of these pathways separately carries the disadvantage that cerebral endopeptidase 24.11 will also be inhibited since thiorphan is capable of crossing the blood-brain barrier (Bourgoin, S., et al, J Pharm Exp Ther (1986) 238:360-366). This disadvantage could be overcome by utilization of a single agent which would block the clearance receptors for ANP, as well as inhibiting the alternate nonsaturatable enzymatic pathway.

The compounds of the invention described herein incorporate endopeptidase 24.11 inhibition functionality (or functionality which inhibits cleavage at Cys105 - Phe106 of ANP) into analogs which also bind the ANP clearance receptors. Surprisingly, the elements which result in cleavage inhibition do not interfere with the clearance receptor binding capability of these compounds.

Disclosure of the Invention

The invention provides compounds which enhance the ability of endogenously secreted ANP hormones to regulate the homeostatic mechanisms which provide protection against high blood pressure and fluid and sodium

retention. Accordingly, the compounds of the invention are useful for the treatment of hypertension, heart disease, renal failure and edema by virtue of their natriuretic, diuretic, and vasorelaxant activities.

Most of the synthetic analog compounds of the present invention retain a core pentapeptide sequence of amino acid residues which correspond in a defined way to the sequence AA_{109}-AA_{113} of native ANPs, using the numbering system recommended by Dzau, V.J., et al, N Engl J Med (1987) 316:1279 for ANP peptides based on the 126-residue proANP peptide. In the known native ANPs, this core sequence is RIDRI in rat and RMDRI in human. While some defined permutations of this sequence, including some wherein AA_{113} is not present, retain activity, most are not active in in vitro model systems for assay of diuretic or natriuretic activities; these analogs empower the function of endogenous ANPs by blocking clearance receptor(s) for these peptides.

In one aspect the invention is directed to compounds of the formula:

$$Z_1Z_2\text{-}AA_{109}\text{-}AA_{110}\text{-}AA_{111}\text{-}AA_{112}\text{-}AA_{113}\text{-}Z_3 \quad (1)$$

wherein:

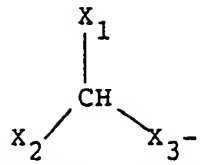
each of AA_{109} and AA_{112} is, independently, preferably a basic/noncyclic, but can be also a neutral/polar/large/nonaromatic amino acid residue; in addition, AA_{109} can be a neutral/nonpolar/large/nonaromatic amino acid;

AA_{110} is a neutral/nonpolar/large/nonaromatic amino acid residue in the D or L configuration;

AA_{111} is an acidic amino acid residue; and

AA_{113} is a neutral/nonpolar/large/nonaromatic amino acid residue, in the D or L configuration or is a covalent bond;

wherein Z_1 is



wherein X_1 is a hydrophobic cyclic or noncyclic residue of 4-14C, X_2 is a substituent containing a metal-coordinating atom within 1.5-7 angstroms (2-4 single covalent bonds) of the illustrated -CH-, said metal-coordinating atom selected from S and O; and $-X_3-$ is a bond, $-CH_2-$, -CO, or -NH-;

Z_2 is a spacer group which provides a spaced dimension of about 4.5-15 angstroms, i.e., contains 3-9 atoms in a linked group or can be conformed to the proper spacing by folding; and

Z_3 is (OH), NH_2, NHR" or NR"R"' wherein R" or R"' are each independently straight or branched chain alkyl of 1-10 carbon atoms wherein 1 or 2 carbons may be replaced by O, N, or S, or Z_3 is a peptide residue of 1-20 amino acid residues, or an amide or alkyl amide thereof, with the proviso that when AA_{113} is a covalent bond, Z_3 cannot be OH, NH_2 or a peptide.

In the foregoing compounds of the invention, one or more of the amide backbone linkages between any adjacent amino acid residues may optionally be replaced by a linkage selected from the group consisting of $-CH_2NH-$, $-CH_2-S-$, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2$ and $-CH_2SO-$.

One or two of the residues in the peptides of the invention may be replaced by the corresponding D isomer, in addition to, or instead of, AA_{110} and AA_{113}.

Also provided in accordance with aspects of the invention are pharmaceutical compositions useful as natriuretics, diuretics, vasodilators and/or modulators of the renin-angiotensin-aldosterone system, which compositions contain at least one compound of the invention,

including the amides and esters and the nontoxic salts thereof, together with a pharmaceutically acceptable liquid, gel or solid carrier.

Additional aspects of the present invention provide methods for producing such compounds and compositions, and methods for using the compounds and compositions as therapeutic agents.

Brief Description of the Drawings

Figure 1 shows the classification of amino acids as they define the compounds of the invention.

Figure 2 shows exemplary embodiments of some preferred Z_1 substituents, along with the abbreviations for them.

Figure 3 shows additional abbreviations for certain embodiments of Z_2

Figure 4 shows exemplary embodiments of the compounds of the invention.

Figure 5 shows the effect of a compound of the invention on diuresis and natriuresis in whole animals.

Modes of Carrying Out the Invention

The class of compounds is capable of exhibiting or modulating the natriuretic, diuretic and/or vasorelaxant activity of the native peptides in mammals in vivo by virtue of the ability to impair the clearance of endogenous ANP both by inhibition of the specific receptor clearance system and by inhibition of endopeptidase 24.11 activity.

The sequence of amino acid residues of the core pentapeptide, and preferred embodiments thereof, is defined in terms of amino acids of certain characteristics of particular subclasses.

Amino acid residues can be generally subclassified into four major subclasses as follows and as shown in Figure 1.

Acidic: The residue has a negative charge due to loss of H ion at physiological pH and the residue is attracted by aqueous solution so as to seek the surface positions in the conformation of a peptide in which it is contained when the peptide is in aqueous medium at physiological pH.

Basic: The residue has a positive charge due to association with H ion at physiological pH and the residue is attracted by aqueous solution so as to seek the surface positions in the conformation of a peptide in which it is contained when the peptide is in aqueous medium at physiological pH.

Neutral/nonpolar: The residues are not charged at physiological pH and the residue is repelled by aqueous solution so as to seek the inner positions in the conformation of a peptide in which it is contained when the peptide is in aqueous medium. These residues are also designated "hydrophobic" herein.

Neutral/polar: The residues are not charged at physiological pH, but the residue is attracted by aqueous solution so as to seek the outer positions in the conformation of a peptide in which it is contained when the peptide is in aqueous medium.

It is understood, of course, that in a statistical collection of individual residue molecules some molecules will be charged, and some not, and there will be an attraction for or repulsion from an aqueous medium to a greater or lesser extent. To fit the definition of "charged", a significant percentage (at least approximately 25%) of the individual molecules are charged at physiological pH. The degree of attraction or repulsion required for classification as polar or nonpolar is arbitrary, and, therefore, amino acids specifically contemplated by the invention have been specifically classified as one or the other. Most amino acids not

specifically named can be classified on the basis of known behavior.

Amino acid residues can be further subclassified as cyclic or noncyclic, and aromatic or nonaromatic, self-explanatory classifications with respect to the side chain substituent groups of the residues, and as small or large. The residue is considered small if it contains a total of 4 carbon atoms or less, inclusive of the carboxyl carbon. Small residues are, of course, always nonaromatic.

For the naturally occurring protein amino acids, subclassification according to the foregoing scheme is as follows (see also Figure 1)

Acidic: Aspartic acid and Glutamic acid;

Basic/noncyclic: Arginine, Lysine;

Basic/cyclic: Histidine;

Neutral/polar/small: Glycine, Serine and Cysteine;

Neutral/polar/large/nonaromatic: Threonine, Asparagine, Glutamine;

Neutral/polar/large/aromatic: Tyrosine;

Neutral/nonpolar/small: Alanine;

Neutral/nonpolar/large/nonaromatic: Valine, Isoleucine, Leucine, Methionine;

Neutral/nonpolar/large/aromatic: Phenylalanine, and Tryptophan.

The gene-encoded amino acid proline, although technically within the group neutral/nonpolar/large/cyclic and nonaromatic, is a special case due to its known effects on the secondary conformation of peptide chains, and is not, therefore, included in this defined group.

Certain commonly encountered amino acids, which are not encoded by the genetic code, include, for example, beta-alanine (beta-Ala), or other omega-amino acids, such as 3-amino propionic, 4-amino butyric and so forth, alpha-aminoisobutyric acid (Aib), sarcosine (Sar), ornithine (Orn), citrulline (Cit), t-butylalanine (t-BuA), t-butylglycine (t-BuG), N-methylisoleucine (N-MeIle), phenylglycine (Phg), and cyclohexylalanine (Cha), norleucine (Nle), cysteic acid (Cya) and methionine sulfoxide (MSO). These also fall conveniently into particular categories.

Based on the above definition,

Sar and beta-Ala are neutral/nonpolar/small;

t-BuA, t-BuG, N-MeIle, Nle and Cha are neutral/nonpolar/large/nonaromatic;

Orn is basic/noncyclic;

Cya is acidic;

Cit, MSO and (acetyl) Lys are neutral/polar/large/nonaromatic; and

Phg is neutral/nonpolar/large/aromatic.

See, also, Figure 1.

The various omega-amino acids are classified according to size as neutral/nonpolar/small (beta-ala, i.e., 3-aminopropionic, 4-aminobutyric) or large (all others).

Other amino acid substitutions for those encoded in the gene can also be included in peptide compounds within the scope of the invention and can be classified within this general scheme.

The nomenclature used to describe analog compounds of the present invention follows the

conventional practice wherein the amino group is assumed to the left and the carboxy group to the right of each amino acid in the peptide. In the formulas representing selected specific embodiments of the present invention, the amino- and carboxy-terminal groups, although often not specifically shown, will be understood to be in the form they would assume at physiological pH values, unless otherwise specified. Thus, the N-terminal H^+_2 and C-terminal-O^- at physiological pH are understood to be present though not necessarily specified and shown, either in specific examples or in generic formulas. However, a shared N linking two residues, where conventional peptide linkage is not present, is shown as [N]. Thus, in designating the substituted N-alkylcarboxy peptides and N-alkylcarboxyhydroxamic acid peptides, the structures are written by indicating the shared nitrogen as -[N]-. (Hydroxylamino in the N-alkylcarboxy hydroxamic peptides is abbreviated HA.) For example, analog #364, which is $HOOC-CH(CH_2Ph)-NH-CH_2CO$-Gly-Arg-Ile-Asp-Arg-Ile-NH_2, where Ph is phenyl, is written as F[N]G-G-R-I-D-R-I-NH_2, and analog #702 which is the compound $HONHCOCH(CH_2Ph)$-NH-CH_2CO-Gly-Arg-Ile-Asp-Arg-Ile-NH_2, is written as HAF[N]G-G-R-I-D-R-I-NH_2.

Additionally, when the peptide chain is not linked through the normal alpha-amino and carboxyl groups to form the peptide bond linking the residues, the following symbols are used: [gamma-L-Glu] denotes peptide linkage through the side-chain carboxyl group of L-Glu and the alpha-carboxyl group now becomes the free carboxylic acid side chain; similarly, the designations [gamma-D-Glu], [beta-L-Asp] and [beta-D-Asp] indicate linkages through the carboxyl not normally included in the peptide linkage.

In the peptides shown, each encoded residue where appropriate is represented by a single letter designation, corresponding to the trivial name of the

amino acid, in accordance with the following conventional list:

Amino Acid	One-Letter Symbol
Alanine	A
Arginine	R
Asparagine	N
Aspartic acid	D
Cysteine	C
Glutamine	Q
Glutamic acid	E
Glycine	G
Histidine	H
Isoleucine	I
Leucine	L
Lysine	K
Methionine	M
Phenylalanine	F
Proline	P
Serine	S
Threonine	T
Tryptophan	W
Tyrosine	Y
Valine	V

The amino acids not encoded genetically are abbreviated as indicated above.

In the specific peptides shown in the present application, the L-form of any amino acid residue having an optical isomer is intended unless otherwise expressly indicated otherwise. While the residues of the invention peptides are normally in the natural L optical isomer form, one or two, preferably one, amino acid in addition to, as well as instead of, AA_{110} and/or AA_{113}, may be

replaced with the optical isomer D form (including embodiments where AA_{110} and AA_{113} are both D).

Free functional groups, including those at the carboxy- or amino-terminus, can also be modified by amidation, acylation or other substitution, which can, for example, change the solubility of the compounds without affecting their activity.

In particular, it has been discovered that carboxyl terminal amide-modified analogs are particularly potent and therefore preferred embodiments of the present invention. In general, the nitrogen atom of the amido group, covalently bound to the carbonyl carbon, will be NH_2, -NHR', or NR'R", wherein R' and R" are straight or branched chain alkyl or alkyl acyl of 1-10C, preferably 1-6C, including these groups wherein 1-2 carbons are replaced by nitrogen, oxygen or sulfur atoms. Representatives of such amido groups are: $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-NHC_6H_5$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH(CH_3)CH_2CH_3$, $-NHCH_2CH_2OH$, $-NHCH_2OCH_2CH_3$ and $-N(CH_3)CH_2CH_2SCH_2CH_3$, among others.

The amidated compounds of the present invention can be synthesized directly, for example using Boc-AA_x-pMBHA-Resin or Boc-AA_x-BHA-Resin, wherein AA_x is the selected carboxy-terminal amino acid of the desired analog compound as described in further detail below. Alternatively, the compounds of the present invention can be chemically or enzymatically amidated subsequent to peptide synthesis using means well known to the art, or prepared by standard solution-phase peptide synthesis protocols.

Preferred Embodiments

A. The Core Pentapeptide

The compounds of the invention all contain the pentapeptide core sequence:

AA_{109}-AA_{110}-AA_{111}-AA_{112}-AA_{113},

wherein each of AA_{109} and AA_{112} is, independently:

a basic/noncyclic; or

a neutral/polar/large/nonaromatic amino acid residue;

in addition, AA_{109} can be a neutral/nonpolar/large/nonaromatic amino acid;

AA_{110} is a neutral/nonpolar/nonaromatic amino acid residue in the D or L configuration;

AA_{111} is an acidic amino acid residue; and

AA_{113} is a neutral/nonpolar/large/nonaromatic amino acid residue in the D or L configuration, or is a covalent bond.

The most preferred sequence of this core is R(I/M)DRI, wherein all residues are in the L configuration and the amino acid residues contained within the parentheses are alternatives. Next in preference are those sequences wherein only one of the R(I/M)DRI residues has been substituted by an alternative residue within the above definitions. Preferred substitutions are:

For AA_{109}, instead of R: K, (Acetyl)K, Q, N, L or Nle;

for AA_{110}, instead of I/M: V, $V^{\dagger}$, L, $L^{\dagger}$, $I^{\dagger}$, $M^{\dagger}$, t-BuA, t-BuG, or Cha;

for A_{111}, instead of D: E or Cya;

for A_{112}, instead of R: K, Q, N, Orn, or Cit;

for A_{113}, instead of I: M, $M^{\dagger}$, V, $V^{\dagger}$, L, $L^{\dagger}$, $I^{\dagger}$, N-MeIle, t-BuA, or a covalent bond.

(The † indicates the D form.)

Particularly preferred are those embodiments wherein this sequence is selected from the group consisting of:

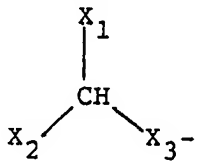
	RM†DRI	R(I/M)DRL
K(I/M)DRI	RLDRI	R(I/M)DRM
Q(I/M)DRI	R(I/M)ERI	R(I/M)DRM†
RVDRI	R(I/M)DKI	R(I/M)DRI†
RI†DRI	R(I/M)DQI	R(I/M)DRV

where the † indicates the D-form of the amino acid preceding it.

More than one alteration from the naturally occurring RIDRI or RMDRI sequence is within the scope of the invention, but less preferred. Particularly favored subsets of this group include those wherein glutamic replaces aspartic as AA_{111} or lysine replaces arginine as AA_{109}, in addition to another substitution.

B. Embodiments of Z_1

Z_1 has the formula



wherein X_1 is a hydrophobic cyclic or noncyclic residue of 4-14C;

X_2 is a substituent containing a metal coordinating atom within 1.5-7 angstroms of the illustrated CH, said metal coordinating atom selected from S and O; and

$-X_3-$ is a bond, $-CH_2-$, -CO-, or -NH-.

In order to provide inhibition of endopeptidase 24.11, both a hydrophobic residue and a metal-coordinating atom must be provided in proximity to each other. Accordingly, X_1 provides the hydrophobicity, and X_2 the metal coordinating atom.

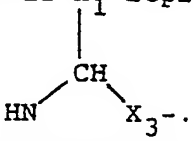
The pivotal CH group is a chiral center; accordingly the invention compounds include those in the R-

and S- configuration or mixtures thereof. In general, the preferred enantiomer will be that wherein the chirality is such that an L-amino acid is mimicked.

$-X_3-$ as shown provides linkage of the two essential features of the Z_1 substituent to the remainder of the compound.

$-X_1$, in preferred embodiments, contains a cyclic or aromatic group conjugated to the illustrated CH through at least one CH_2, NH, O, or S linking group. Occasionally, this linking group may contain two members and thus includes $-OCH_2-$, $-CH_2O-$, $-CH_2S-$, $-SCH_2-$, $-CH_2CH_2-$, $-NHCH_2-$, or $-CH_2NH-$. The aromatic substituent may be phenyl, indolyl, biphenyl, naphthyl, pyridyl, imidazole, and the like, i.e., any 5-12 member ring system which can include one or two heteroatoms selected from N, O and S. In addition, the hydrophobic moiety may be nonaromatic such as, for example, cyclohexyl or any 5-10 membered nonaromatic ring system including one or two N, S or O heteroatoms. In some instances, the hydrophobic moiety may also be noncyclic.

$-X_2$, which contains the metal-coordinating atom, effects the appropriate separation of said atom from the illustrated CH. This separation is basically the space provided by 2-4 covalent bonds, or about 1.5-7A°, and thus, $-X_2$ is exemplified by $-CH_2SH$, $-CH_2CH_2SH$, -COOH, -CONHOH, $-CH_2COOH$, $-CH_2CONHOH$, $-NHCH_2COOH$, -NHCHRCOOH, where R is $-CH_2Ph$ or $-CH_2CH_2Ph$, and $NHPO(OR')_2$ wherein each R' is independently H or alkyl (1-7C). When $-X_2$ is $-NHCH_2COOH$, -NHCHRCOOH, or $-NHPO(OR')_2$, the "N" will be bracketed [N] if X_1 represents an amino acid residue.



Illustrative and preferred embodiments of Z_1 (along with abbreviations therefor) are shown in Figure 2. Especially preferred are compounds wherein Z_1 is such that

X_3 is CO and X_2 is CH_2SH, or X_3 is CO and X_2 is CONOH, or X_3 is CO and X_2 is $-CH_2CONHOH$ or X_3 is CO and X_2 is [N]CHRCOOH where R is CH_2Ph or CH_2CH_2Ph.

The illustrated CH is conjugated to the remainder of the compound of the invention through the linker $-X_3-$. The linker may simply be a bond to the spacer described as Z_2 or may be selected from -NH-, -CO-, and $-CH_2-$. When the spacer Z_2 is terminated by an amino acid residue, the structures illustrated below may show the NH which forms the N-terminus of the peptide as [N] i.e. N in brackets for convenience in decipherment.

C. Embodiments of Z_2

In the compounds of the invention, Z_2 provides a spacer element separating AA_{109} from Z_1. The linker Z_2 must be capable to achieve a distance between AA_{109} and Z_1 of about between 4.5 and 15 angstroms, corresponding to 3-9 atoms in a normally extended chain. Of course, longer linkers can be used provided their three-dimensional conformations permit this spacing distance to be accommodated.

Preferred embodiments for Z_2 are selected from the group consisting of

(a) $(AA)_a$ wherein AA is an amino acid and "a" is 1 or 2, especially wherein each AA is selected from G, S, A, D-Ala, Sar, Aib, Asp, Glu, D-Asp, D-Glu, beta-L-Asp, beta-D-Asp, gamma-L-Glu, and gamma-D-Glu (in gamma-Glu and beta-Asp linkage is through the side-chain carboxyl);

(b) $-(P)_n-(CO)_x-$ wherein x is 0 or 1, n is 1-6, and P is CH_2, wherein 1-2 of said $-CH_2-$ groups can be replaced by NH, provided N-N does not occur; and

(c) $-(Q)_m-B-(Q)_m-(CO)_x-$ wherein x is 0 or 1, each m is independently 0-3 but the sum of both m is 5 or less; Q is CH_2 or NH, with the proviso that -N-N- does not occur, and B is a saturated or unsaturated five- or six-membered ring optionally containing an N heteroatom.

Particularly preferred embodiments of Z_2 are shown in Figure 3. These include 4-aminobenzoyl(4-AB); 4-aminophenyl acetyl (4-APA); 4-piperidine carboxyl (4-PIP) and 4-aminomethyl cyclohexoyl (4-AMC).

D. Embodiments of Z_3

Preferred for Z_3 are NH_2, NHR", and the amide or alkyl amide of peptide residues of 1-3 amino acids. Especially preferred among the embodiments which are peptide residues are those wherein the amino acids are selected from G, A, and S. In particular, however, when AA_{113} is a covalent bond, Z_3 should be in the alkyl amidated form, e.g., -NHR" wherein R' is 2-10C.

E. Nonpeptide Linkages

In one embodiment of the invention, the amide linkages (-CO-NH-) within the core pentapeptide or those described above within Z_1 and/or Z_2 and/or Z_3 can be replaced with other types of linkages such as $-CH_2NH-$, $-CH_2-S-$, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-C(OH)CH_2-$ and $-CH_2SO-$, by methods known in the art. The following references describe preparation of peptide analogs which include these alternative-linking moieties: Spatola, A.F., Vega Data (March 1983), Vol. 1, Issue 3, "Peptide Backbone Modifications" (general review); Spatola, A.F., in "Chemistry and Biochemistry of Amino Acids Peptides and Proteins", B. Weinstein, ed., Marcel Dekker, New York, p. 267 (1983) (general review); Morley, J.S., Trends Pharm Sci (1980) pp. 463-468 (general review); Hudson, D., et al, Int J Pept Prot Res (1979) 14:177-185 (-CH2NH-, $-CH_2CH_2-$); Spatola, A.F., et al, Life Sci (1986) 38:1243-1249 ($-CH_2-S$); Hann, M.M., J Chem Soc Perkin Trans I (1982) 307-314 (-CH-CH-, cis and trans); Almquist, R.G., et al, J Med Chem (1980) 23:1392-1398 ($-COCH_2-$); Jennings-White, C., et al, Tetrahedron Lett (1982) 23:2533 ($-COCH_2-$); Szelke, M., et al, European Ap-

plication EP 45665 (1982) CA: 97: 39405 (1982) (-CH(OH)CH_2-); Holladay, M.W., et al, Tetrahedron Lett (1983) 24:4401-4404 (-C(OH)CH_2-); and Hruby, V.J. Life Sci (1982) 31:189-199 (-CH_2-S-).

F. Preferred Embodiments of the Invention Analogs

Preferred analogs of the invention are shown in Figure 4.

In the figure, in compounds 1-88, the core sequence is R-I-D-R-I, Z_3 is NH_2, Z_2 is AA_a, and Z_1 contains a mercaptyl group, where X_2- is -CH_2SH.

Compounds 89-110 are similar except that Z_2 is of the formula -$(P)_n$-(CO)- wherein n is 4-5.

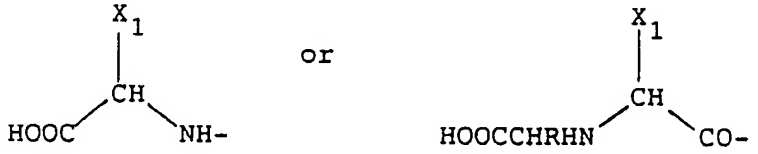
Compounds 111-154 are similar except that Z_2 is selected from 4-AB, 4-AMC, 4-APA, and 4-PIP.

Compounds 155-220 are similar except that they have the core sequence K-I-D-R-I, Z_3 is NH_2.

Compounds 221-286 are similar except that they have core sequences R-I-D-R - NHR" wherein R" is $CH_2CH(CH_3)CH_2CH_3$.

Compounds 287-363 return to the R-I-D-R-I core peptide, Z_3 as NH_2, and embodiments of Z_1 wherein X_2 is -CH_2CH_2SH.

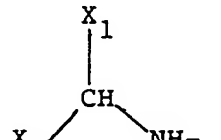
Compounds 364-624 all have the core sequence R-I-D-R-I with Z_3 as NH_2 in various preferred embodiments for Z_2, but Z_1 no longer contains a mercaptyl. Z_1 is selected from F[N], BF[N], Nal2[N], Nal1[N], Cha[N], W[N], homoF[N], homoCha[N], homoNal2[N], F[N]F, F[N]BF, F[N]Nal2, F[N]Nal1, F[N]Cha, F[N]W, F[N]homoF, F[N]homoCha, F[N]homoNal2, and similar structures wherein homoF[N] or G[N] substitutes for F[N]. Thus, in these embodiments Z_1 is



wherein R is -H, $-CH_2Ph$ or $-CH_2CH_2Ph$.

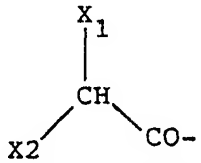
In compounds 625-701, Z_1 also contains a carboxyl group and is selected from embodiments wherein X_2- is COOH, and $-X_3-$ is -CO-.

In compounds 702-764, X_2- contains a hydroxamate and Z_1 is



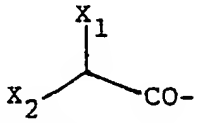
where X_2- is -CONHOH.

In compounds 765-841 Z_1 is



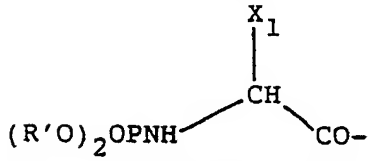
where X_2 is -CONHOH.

In compounds 842-918, Z_1 is



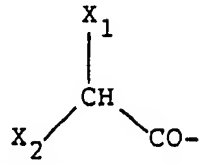
where X_2- is $-CH_2CONHOH$.

In compounds 919-981, Z_1 is



wherein X_1 is variable and X_2 is phosphoramidate as shown. In these embodiments, the various substituents shown in Figure 2 for Z_1 which are aromatic amino acids are conjugated to the Z_2 substituent through their alpha-carboxyl groups and are phosphorylated at the alpha-amino groups. Thus, Z_1 has the structure shown as embodiments Z19-Z27 of Figure 2.

In compounds 982-1056, Z_1 has the formula



wherein X_1 is variable and X_2 is $-CH_2COOH$.

Especially preferred are compounds 1-286, 436-561, and 842-981, inclusive.

Compound 122 is particularly preferred.

Synthesis

Compounds within the scope of the present invention can be synthesized chemically by means well known in the art such as, e.g., solid-phase peptide synthesis. The synthesis is commenced from the carboxy-terminal end of the peptide using an alpha-amino protected amino acid. t-Butyloxycarbonyl (Boc) protective groups can be used for all amino groups even though other protective groups are suitable. For example, Boc-Ile-OH, Boc-Arg-OH, Boc-Asp-OH, Boc-Ile-OH or Boc-Arg-OH (i.e., selected analog carboxy-terminal amino acids) can be esterified to chloromethylated polystyrene resin supports, preferably of p-methyl benzhydryl amine (pMBHA) resin. The polystyrene resin support is preferably a copolymer of styrene with about 0.5 to 2% divinyl benzene as a cross-linking agent which causes the polystyrene polymer to be completely insoluble in certain organic solvents. See Stewart, et al, Solid-Phase Peptide Synthesis (1969) W.H. Freeman Co., San Francisco and Merrifield, J Am Chem Soc (1963) 85:2149-2154. These and other methods of peptide synthesis are also exemplified by US Patent Nos. 3,862,925, 3,842,067, 3,972,859, and 4,105,602.

The synthesis may use manual techniques or automatically employing, for example, an Applied BioSystems 430A Peptide Synthesizer (Foster City, California) or a Biosearch SAM II automatic peptide

synthesizer (Biosearch, Inc. San Rafael, California), following the instructions provided in the instruction manual supplied by the manufacturer.

It will be readily appreciated by those having ordinary skill in the art of peptide synthesis that the intermediates which are constructed in accordance with the present disclosure during the course of synthesizing the present analog compounds are themselves novel and useful compounds and are thus within the scope of the invention.

Administration and Use

Compounds of the present invention are shown to have natriuretic, diuretic and hypotensive activity in the intact mammal, and may possess vasorelaxant activity or inhibit the release of aldosterone and renin.

Thus these compounds, and compositions containing them, can find use as therapeutic agents in the treatment of various edematous states such as, for example, congestive heart failure, nephrotic syndrome and hepatic cirrhosis, pulmonary disease, in addition to hypertension and renal failure due to ineffective renal perfusion or reduced glomerular filtration rate.

Thus the present invention also provides compositions containing an effective amount of compounds of the present invention, including the nontoxic addition salts, amides and esters thereof, which may, alone, serve to provide the above-recited therapeutic benefits. Such compositions can also be provided together with physiologically tolerable liquid, gel or solid diluents, adjuvants and excipients.

These compounds and compositions can be administered to mammals for veterinary use, such as with domestic animals, and clinical use in humans in a manner similar to other therapeutic agents. In general, the dosage required for therapeutic efficacy will range from about 0.01 to 1000 mcg/kg, more usually 0.1 to 1000 mcg/kg

of the host body weight. Alternatively, dosages within these ranges can be administered by constant infusion over an extended period of time until the desired therapeutic benefits have been obtained.

Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation may also be emulsified. The active ingredient is often mixed with diluents or excipients which are physiologically tolerable and compatible with the active ingredient. Suitable diluents and excipients are, for example, water, saline, dextrose, glycerol, or the like, and combinations thereof. In addition, if desired the compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, stabilizing or pH-buffering agents, and the like.

The compositions are conventionally administered parenterally, by injection, for example, either subcutaneously or intravenously. Additional formulations which are suitable for other modes of administration include suppositories, intranasal aerosols, and, in some cases, oral formulations. For suppositories, traditional binders and excipients may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10% preferably 1%-2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained-release formulations, or powders, and contain 10%-95% of active ingredient, preferably 25%-70%.

The peptide compounds may be formulated into the compositions as neutral or salt forms. Pharmaceutically

acceptable nontoxic salts include the acid addition salts (formed with the free amino groups) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or organic acids such as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

In addition to the compounds of the present invention which display natriuretic, diuretic or vasorelaxant activity, compounds of the present invention can also be employed as intermediates in the synthesis of such useful compounds. Alternatively, by appropriate selection, compounds of the present invention whose activity levels are reduced or eliminated entirely can serve to modulate the activity of other diuretic, natriuretic or vasorelaxant compounds, including compounds outside the scope of the present invention, by, for example, binding to alternate receptors, stimulating receptor turnover, or providing alternate substrates for degradative enzyme or receptor activity and thus inhibiting these enzymes or receptors. When employed in this manner, such compounds can be delivered as admixtures with other active compounds or can be delivered separately, for example, in their own carriers.

Compounds of the present invention can also be used for preparing antisera for use in immunoassays employing labeled reagents, usually antibodies. Conveniently, the polypeptides can be conjugated to an antigenicity-conferring carrier, if necessary, by means of dialdehydes, carbodiimide or using commercially available linkers. These compounds and immunologic reagents may be labeled with a variety of labels such as chromophores, fluorophores such as, e.g., fluorescein or

rhodamine, radioisotopes such as ^{125}I, ^{35}S, ^{14}C, or ^{3}H, or magnetized particles, by means well known in the art.

These labeled compounds and reagents, or labeled reagents capable of recognizing and specifically binding to them, can find use as, e.g., diagnostic reagents. Samples derived from biological specimens can be assayed for the presence or amount of substances having a common antigenic determinant with compounds of the present invention. In addition, monoclonal antibodies can be prepared by methods known in the art, which antibodies can find therapeutic use, e.g., to neutralize overproduction of immunologically related compounds in vivo.

Examples

The following examples are provided by way of illustration, rather than implying any limitation of the subject invention.

Compounds of the present invention were synthesized by solid-phase techniques performed manually or, alternatively, on an Applied BioSystems 430A Peptide Synthesizer (Foster City, California) or a Biosearch Sam II automated peptide synthesizer (Biosearch, San Rafael, California) using t-Boc amino acids in accordance with the instructions of the manufacturer.

Residues Z_2-AA_{109}-AA_{113} are commonly prepared on solid-phase supports using conventional t-Boc chemistry. Where applicable, Z_2 spacers are incorporated into the peptide chain using BOC-Z_2 protected intermediates that are conveniently prepared from the corresponding NH_2-Z_2-COOH and Boc-anhydride. The spacers are coupled to the free amino group on the growing peptide chain using standard carboxyl activating agents such as dicyclohexylcarbodiimide (DCC). For peptides which contain the 3-mercapto-2-(substituted)-propionyl, examples

(1-286), or 4-mercapto-2-(substituted)-butyryl amino terminus, examples (287-363), the corresponding protected 3-Acetylthio- or 3-Benzoylthio-2-(substituted)-propionic or 4-acteylthio or 4-Benzoylthio-2-(substituted)- butyric acids are used. The S-acetyl or S-benzoyl groups later removed by base hydrolysis as described by Fournie-Zaluski et al, Eur J Biochem (1984) 139:267-274. For examples containing the substituted malonoyl or succinoyl groups, examples (625-918), generally the methods found in Fournie-Zaluski et al, J Med Chem (1985) 28:1158-1169 can be used for their incorporation into the peptide-resins. For peptides containing the (N-hydroxy)carboxamido-2-(substituted)-1-oxo-acetyl group referred to as hydroxyamino malonoyl and 3-(N-hydroxy)carboxamido-2-(substituted)-1-oxo propyl groups referred to as hydroxyamino succinoyl groups, these groups can be introduced according to the methods outlined in Fournie-Zaluski, supra, and in Fr. patent 81.23.488. The N-carboxyalkyl-containing peptides, examples (364-624), are prepared using the methods of Fournie-Zaluski et al, J Med Chem (1983) 26:60-65, Patchett et al, Nature (1980) 288:280-283, or Mumford et al, Biochem Biophys Res Commun (1982) 109:1303-1309. N-alkylation is routinely carried out with the corresponding substituted alpha-ketocarboxylic acid or ester by reductive amination of the free amino group on the peptide resin. N-Phosphoryl peptides, examples (919-981), can be obtained using the procedures outlined in Kam et al, Biochemistry (1979) 18:3032-3038.

Procedure A

Preparation of Boc-AA1.....AAn-1-AAn-O-Polystyrene Resin

One gram of selected Boc-AA_n-O-Polystyrene-Resin (0.2-0.6 mmole/g resin) (obtainable from, e.g., Peninsula Labs, Inc.) is treated according to schedule A for incorporation of the Boc-AA_{n-1}-OH.

Schedule A

1) Wash 3x with dichloromethane (CH_2Cl_2);
2) Treat for 1 min with TFA:CH_2Cl_2:ethane dithiol (EDT) (45:50:5 by volume);
3) Treat for 20 min. with TFA:CH_2Cl_2:EDT (45:50:5 by volume);
4) Wash 3x with CH_2Cl_2;
5) Treat 2x for 1 min. 10% (v/v) Diisopropylethylamine (DIPEA) in CH_2Cl_2;
6) Wash 2x with CH_2Cl_2;
7) Wash 2x with methanol (MeOH);
8) Repeat (5-7) once;
9) Wash 3x with CH_2Cl_2;
10) Add 1-6 equivalents of preformed symmetrical anhydride of the suitably protected Boc-amino acid dissolved in CH_2Cl_2 or dimethyl formamide (DMF)/CH_2Cl_2 (50:50 volume), (Boc-Asn-OH, Boc-Gln-OH and Boc-Arg(TOS)-OH were coupled as active esters using N-hydroxybenxotriazole);
11) Wash 2x with CH_2Cl_2;
12) Wash 2x with 10% DIPEA;
13) Wash 2x with CH_2Cl_2;
14) Wash 2x with MeOH;
15) Wash 2x with CH_2Cl_2;
16) Repeat steps (11-15) once;
17) Test by ninhydrin reaction according to Kaiser et al, Anal Biochem 34:595 (1970). If the coupling reaction was incomplete, repeat steps (10-16) or, alternatively, cap synthesis using N-acetyl imidazole (0.30 M in DMF) or an excess of acetic anhydride in CH_2CL_2.

Procedure B

Preparation of Boc-AA_n-p-Methylbenzhydrylamine resin

The selected Boc-AA_n-OH is attached to a p-Methylbenzhydrylamine (pMBHA) resin via N,N'-dicyclohexylcarbodiimide, as described below.

Schedule B

1) Wash the pMBHA HCl resin;
2) Wash the resin 2x with 10% (v/v) DIPEA in CH_2Cl_2;
3) Wash 2x with CH_2Cl_2;
4) Wash 2x with MeOH;
5) Wash 2x with CH_2Cl_2;
6) Add 1-6 equivalents of preformed symmetrical anhydride of the suitably protected Boc-amino acid dissolved in CH_2Cl_2, with reaction time of 0.5-24 hrs.

Unreacted amino groups are acetylated with 0.30/M N-acetylimidazole:DMF, or acetic anhydride:CH_2Cl_2.

The following examples demonstrate the chemical synthesis of representative analog compounds (identified as Analog #) which illustrate certain aspects of the present invention.

Example 1

Preparation of Analog #1:

MBP-G-G-R-I-D-R-I-NH_2

One gram of pMBHA resin (0.25 meq/g, Applied Biosystems, Foster City, CA) was subjected to procedure B followed by schedule A with the required sequence of amino acids (introduced in order as Boc-Ile-OH, Boc-Arg(Tos)-OH, Boc-Asp(O-cHexyl)-OH, Boc-Ile-OH, Boc-Arg(Tos)-OH, Boc-Gly-OH). After deprotection of the Boc- group followed by neutralization, the MBP-G- group was added using a carboxyl activated form of (D,L)-thiorphan. This was

accomplished by treatment of (D,L)-thiorphan (100 mg, 0.39 mmol, Bachem Biosciences, Philadelphia, PA) with N-hydroxybenzotriazole (0.39 mmol, 1 eq) and 1 eq of 1 M DCC in CH_2Cl_2 to form the activated ester of (D,L)-thiorphan which was reacted with the deprotect peptide resin in 50/50 CH_2Cl_2/DMF for 4 hr. The resin was washed 3x with CH_2Cl_2 and twice with MeOH and dried in vacuo.

The peptide resin was treated with anhydrous hydrogen fluoride (HF) containing 10% anisole, 2% ethyl methyl sulfide for 30 min. at -10°C, and an additional 30 min. at 0°C. The HF was removed in vacuo and the peptide/resin mixture was suspended in diethyl ether followed by alternately washing with chloroform and ether 3x. After a final ether wash, the peptide was extracted from the resin with 2.0 M acetic acid, diluted with distilled water and lyophilized.

Purification of the crude peptide was achieved by desalting on Sephadex G-25F (Pharmacia) using 0.5 M acetic acid as eluant, followed by cation exchange chromatography on CM-Sepharose (Pharmacia) or CM-cellulose (Whatman) using an elution gradient of NH_4OAc. Fractions were analyzed by reversed-phase liquid chromatography on a Vydac C18 column using a 15-35% acetonitrile gradient containing 0.1% trifluoroacetic acid (TFA). Semi-preparative HPLC gave purified peptide #1 as judged by amino acid analysis.

Example 2

Preparation of Analog #445:

F[N]F-4-APA-R-I-D-R-I-NH_2

One gram of pMBHA resin (0.45 meq/g, U.S. Biochemical) was subjected to procedure B followed by schedule A with the required sequence of amino acids (introduced in order as Boc-Ile-OH, Boc-Arg(Tos)-OH, Boc-Asp(O-cHexyl)-OH, Boc-Ile-OH, Boc-Arg(Tos)-OH, Boc-p-aminophenylacetic acid (Boc-4-APA-OH), Boc-Phe-OH). Fol-

lowing deprotection of the Boc-group and neutralization, reductive amination of the free amine was conducted by treatment with phenylpyruvic acid (246 mg, 1.5 meq, Aldrich) in the presence of catalytic acetic acid (100 ul) and 95 mg of $NaCNBH_3$ in DMF at room temperature for 1 day. The resin was then washed with DMF and CH_2Cl_2 extensively, followed by MeOH and dried in vacuo.

The peptide resin was treated with anhydrous hydrogen fluoride (HF) containing 10% anisole, 2% ethyl methyl sulfide for 30 min. at -10°C, and an additional 30 min. at 0°C. The HF was removed in vacuo and the peptide/resin mixture was suspended and stirred with diethyl ether for 20 min. This mixture was alternately washed with chloroform and ether 3x. After a final ether wash, the peptide was extracted from the resin with 2.0 M acetic acid, diluted with distilled water and lyophilized.

Purification of the crude peptide was achieved by cation exchange chromatography on CM-Sepharose (Pharmacia) or CM-cellulose (Whatman) using an elution gradient of NH_4OAc. Final purification of the peptide was accomplished by semi-preparative HPLC on a Vydac C18 column using a 15-35% acetonitrile gradient containing 0.1% TFA. Amino acid analysis confirmed the structure of peptide #445.

Example 3

Binding to ANP Clearance Receptor

The assay systems used are adapted from those of Schenk, D.B., et al, Biochem Biophys Res Commun (1985) 127:433-442 and Scarborough, R.M., J Biol Chem (1986) 261:12960-12964. These assays measure clearance receptor binding affinity through competition with ANP using the receptors on bovine aortic smooth muscle (BASM) or bovine aortic endothelial (BAE) cells. Also employed is the receptor binding affinity assay for the clearance receptor

in isolated perfused rat kidney as described by Maack, T., et al, Science (1987) 238:675-679.

Illustrative compounds of the invention were tested in the BASM assay using I^{125} labeled rANP (102-126) with the iodine substituted at the tyrosine at 126. The results shown as the concentration at which 50% maximal binding of the labeled standard to BASM cells is displaced is designated Ki(app). Thus, the lower the Ki(app), the more effective the binding of the analog.

Table 1 shows the results of this competition binding assay with the concentration of analog required for half-maximal inhibition of ANP binding as Ki(app) in units of nanomoles/liter.

Table 1

BASM Receptor Binding Assay

Analog	Structure	Ki(app)(nM)
	rANP(102-126)	7.5
12	MBP-D-G-R-I-D-R-I-NH_2	207.4
23	MBP-[D-Asp]-G-R-I-D-R-I-NH_2	115.4
78	MBP-[-Glu]-R-I-D-R-I-NH_2	201.8
122	MBP-4-APA-R-I-D-R-I-NH_2	10.9
364	F-[N]-G-G-R-I-D-R-I-NH_2	66.9
427	F-[N]-[beta-Ala]-G-R-I-D-R-I-NH_2	11.5
436	F-[N]-F-G-G-R-I-D-R-I-NH_2	27.3
445	F-[N]-F-4-APA-R-I-D-R-I-NH_2	6.5
463	F-[N]-F-D-G-R-I-D-R-I-NH_2	225.4
544	homoF-[N]-F-[-Glu]-R-I-D-R-I-NH_2	58.2
702	HAF-[N]-G-G-R-I-D-R-I-NH_2	4.6
1	MBP-G-G-R-I-D-R-I-NH_2	19.6

In the rat kidney receptor binding assay, the native 28-residue labeled ANP was used: I^{125} labeled rANP(99-126), with the label linked to tyrosine at 126. The results of this assay are shown in Table 2 as the ratio of bound-to-free labeled rANP(99-126) in the pres-

ence and absence of competing compound. As shown in Table 2, analog 436 successfully competes with the labeled compound for receptor.

Table 2

Ratio of Bound/Free (^{125}I)rANP(99-126)

Compound	Whole Kidney
labeled compound (4×10^{-12}M) (n = 8)	59 ± 16
labeled compound (4×10^{-12}M) + rANP(99-126) (1×10^{-6}M) (n = 2)	0.56
labeled compound (4×10^{-12}M) + #436 (1×10^{-6}M) (n = 2)	1.31

Example 4

Inhibition of Endopeptidase 24.11

Endopeptidase 24.11 inactivates ANP by cleavage at the Cys^{105}-Phe^{106} amide bond. The ability of the compounds of the invention to inhibit this degradation was assayed by a modification of the procedure of Ura, N., et al, Kidney Int (1987) 32:507-513 by substituting rANP(99-126) for bradykinin as a substrate.

Briefly, rat urine was collected and desalted on Sephadex G-25 as described by Ura (supra) and 4 ul of sample in 100 ul 0.1 M Tris buffer, pH 7.2 containing

aminopeptidase inhibitor bestatin (10 ug/ml), potato tuber carboxy peptidase inhibitor (10 ug/ml) and aprotinin (5,000 kalikrein inhibitory unit/ml) were incubated for 15 min at 37°C. The assay was then initiated by addition of 2-10 ug rANP(99-126) to a final volume of 0.5 ml and incubated at 10-20 min at 37°C. Termination of the reaction was accomplished by boiling, spinning and freezing.

Compounds to be tested for their ability to inhibit the endopeptidase were added to the preincubation mixture 15 min before addition of substrate.

The frozen samples, incubated with or without inhibitor, were thawed and analyzed by HPLC to determine the concentration of starting rANP(99-126) and its degradation product. HPLC analysis was conducted on Vydac C18 reverse phase HPLC column (4.6 mm ID x 12.5 cm; 5 uM, 300A). A linear gradient of 15-35% acetonitrile containing 0.1% TFA was run at 1.0 ml/min on a Perkin-Elmer series 4 HPLC system. The effluent was monitored at 220 nm and the peptide peak heights measured.

The results were computed as the percent of the Cys^{105}-Phe^{106} cleavage metabolite peak in the test sample as compared to the peak height for this metabolite in the control. The results are shown in Table 3.

Table 3

% Inhibition of Metabolite Formation

Dose	Thiorphan	Phosphoramidon	122	1	526	445
10 uM	92	97	97	92	20	0
1 uM	67	80	72	45	0	-
100 nM	53	30	25	23	-	-
20 nM	12	0	12	0	-	-

As shown in Table 3, analog #1 of the invention, though less potent than thiorphan as an inhibitor, is capable of inhibition with an ED_{50} of approximately 1 uM.

Furthermore, analog #122 is only slightly less potent than thiorphan and is comparable to phosphoramidon.

Example 5

In Vivo Assays

The ability of analog #1 to effect diuresis and natriuresis in whole animals was determined as follows. Female Sprague-Dawley rats (230-260 g) anesthetized with inactin (100 mg/kg body weight) were catheterized by placing cannulae in femoral artery (B.P. monitoring), femoral vein (infusion of drugs and saline) and bladders (collection of urine). Post surgery, and prior to administration of test substance, saline was infused at 20 ul/min for 45 min in order to stabilize urine flow. Stabilization of urine flow was determined by collection of urine during several 10 min periods. Once stable urine flow was obtained, three 10 min control periods were collected followed by infusion of test compounds at 20 ul/min for 1 hr after priming with 10 times the infusion dose. Following experimental infusion period, saline was infused at 20 ul/min for 2 additional hr during the recovery phase. The urine volume collected during ten minute collection periods was determined gravimetrically. Urinary sodium excretion $U_{Na}V$ was determined photometrically. For comparison, Table 4 shows the effects of 300 ng/kg/min infusion of hANP(102-126) and compound #1.

Table 4

Comparative Effects of hANP(102-126) and #437 in Rats

	V(ul/min)	$U_{Na}V$(uEq/min)
hANP(102-126) 300 ng/kg/min	16.8±9.3	2.24±0.77
#1 10 ug/kg/min	11.6±2.7	3.72±1.1
Control Saline	3.5±1.0	0.13±0.04

Differences (_) between experimental and control periods (mean ± SE) in rats infused with compound (n=7).

The specific effects of compounds on natriuresis and diuresis in anesthetized rats are shown in Figures 5A-5D. Percent and absolute increase ± SE for natriuresis and diuresis are displayed in these figures. Analog #1 infused at 10 ug/kg/min gives a mean 10-fold increase in urinary sodium excretion and a 2- to 3-fold increase in urinary flow rate. Maximal effects are not observed until the second or third experimental collection period and are sustained through the infusion. Slow return to baseline urine flow and sodium excretion rates are observed for Analog #1 compared to effects with ANP(102-126) and are consistent with the concept that clearance mechanisms once inhibited require significant time before they can fully participate in ANP clearance.

Claims

1. A linear peptide compound having natriuretic, diuretic and/or vasodilator activity in mammals, which has the formula:

$$Z_1Z_2\text{-}AA_{109}\text{-}AA_{110}\text{-}AA_{111}\text{-}AA_{112}\text{-}AA_{113}\text{-}Z_3 \quad (1)$$

wherein:

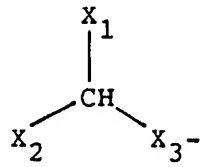
each of AA_{109} and AA_{112} is, independently, a basic/noncyclic or neutral/polar/large/nonaromatic amino acid residue; and AA_{109} can also be a neutral nonpolar/large/nonaromatic amino acid residue;

AA_{110} is a neutral/nonpolar/large/nonaromatic amino acid residue in the D or L configuration;

AA_{111} is an acidic amino acid residue;

AA_{113} is a neutral/nonpolar/large/nonaromatic amino acid residue in the D or L configuration or a covalent bond; and

wherein Z_1 is



wherein X_1 is a hydrophobic cyclic or noncyclic residue of 4-14C, X_2 is a substituent containing a metal coordinating atom within 1.5-7 angstroms of the illustrated -CH-, said metal-coordinating atom selected from S and O, and $-X_3-$ is a bond, $-CH_2-$, -CO, or -NH-;

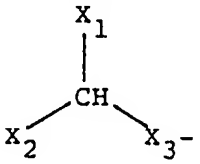
Z_2 is a spacer group capable of providing a spaced dimension of 4.5-15 angstroms between AA_{109} and the hydrophobic moiety of Z_1;

Z_3 is (OH), NH_2, NHR" or NR"R"' wherein R" or R"' are each independently straight or branched chain alkyl of 1-10 carbon atoms wherein 1 or 2 carbons may be

replaced by O, N, or S; or is a peptide of 1-20 amino acid residues, or an amide or alkyl amide thereof; but when AA_{113} is a covalent bond, Z_3 cannot be (OH), NH_2 or a peptide; and

wherein one or more of the amide linkages between adjacent amino acid residues may optionally be replaced by a linkage selected from the group consisting of $-CH_2NH-$, $-CH_2S-$, $-CH_2CH_2-$, $-CH=CH-$, $-COCH_2-$, $-CH(OH)CH_2-$ and $-CH_2SO-$.

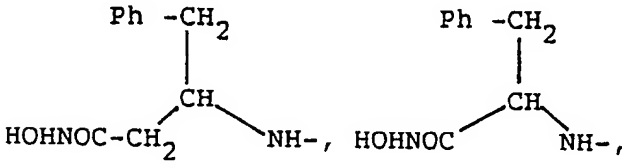
2. The compound of claim 1 wherein Z_1 is

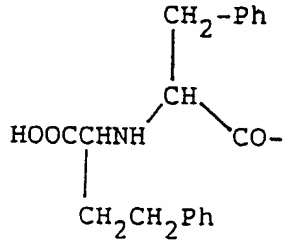


wherein X_1 comprises a cyclic (5-12 member) aromatic or nonaromatic group conjugated through at least one CH_2, NH, O or S linking group; and

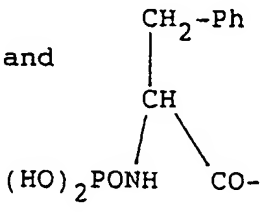
$-X_2$ is selected from $-CH_2SH$; $-CH_2CH_2SH$; -COOH; $-CH_2COOH$; CHRCOOH; wherein R is $-CH_2Ph$ or $-CH_2CH_2Ph$, wherein Ph is phenyl; -CONHOH; $-CH_2CONHOH$; $-NHCH_2COOH$; and $-NHPO(OR')_2$ wherein each R' is independently H or alkyl (1-7C).

3. The compound of claim 2 wherein Z_1 is selected from the group consisting of





and



4. The compound of claims 1-3 wherein Z_2 is selected from the group consisting of

(a) $-(AA)_a-$ wherein AA is an amino acid and a is 1 or 2;

(b) $-(P)_n-(CO)-_x$ wherein x is 0 or 1, n is 1-6, and P is CH_2 wherein 1-2 of said $-CH_2-$ groups can be replaced by NH, provided N-N does not occur; and

(c) $-(Q)_m-B-(Q)_m-(CO)_x-$ wherein x is 0 or 1, each m is 0-3, wherein the sum of m is 5 or less, -B- is a saturated or unsaturated five- or six-membered ring optionally containing an N heteroatom, and Q is CH_2 or NH, provided -N-N- does not occur.

5. The compound of claims 1-4 wherein Z_3 is NH_2 or NHR", or a peptide of 1-2 amino acid residues or the amide or alkyl amide form thereof.

6. The compound of claims 1-5 wherein AA_{109}-AA_{110}-AA_{111}-AA_{112}-AA_{113} is R(I/M)DRI and at most one residue therein is replaced by substituting

K, acetyl K, Q, N, L or NMeIle for R as AA_{109};

V, $V^{\dagger}$, L, $L^{\dagger}$, $I^{\dagger}$, $M^{\dagger}$, t-BuA, t-BuG or Cha for I or M as AA_{110};

E for D as A_{111};

Q, N, K, Orn or Cit for R as A_{112}; and

M, $M^{\dagger}$, V, $V^{\dagger}$, L, $L^{\dagger}$, $I^{\dagger}$, P, N-MeIle, t-BuA or a covalent bond for I as AA_{113},

wherein † indicates the D form.

7. The compound of claim 6 wherein AA_{109}-AA_{110}-AA_{111}-AA_{112}-AA_{113} is selected from the group consisting of:

K(I/M)DRI

Q(I/M)DRI

RVDRI
RI†DRI
RM†DRI
RLDRI
R(I/M)ERI
R(I/M)DKI
R(I/M)DQI
R(I/M)DRL
R(I/M)DRM
R(I/M)DRM†
R(I/M)DRI†
R(I/M)DRV and
R(I/M)DRI

wherein † indicates the D form of the amino acid preceding it.

8. The compound of claims 1-7 wherein one or more of the amide linkages between adjacent amino acid residues may be replaced by a linkage selected from the group consisting of $-CH_2NH-$, $-CH_2S-$, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$ and $-CH_2SO-$.

9. The compound of claims 1-8 wherein Z_1 is selected from the substituents of Figure 2.

10. The compound of claims 1-9 wherein Z_2 is selected from -G-G-, -D-G-, [D-Asp]-G-, D-or L-gamma-Glu, D- or L-beta-Asp, 4-AB, 4-APA, 4-PIP and 4-AMC.

11. The compound of claims 1-10 wherein AA_{109}-AA_{110}-AA_{111}-AA_{112}-AA_{113}-Z_3 is R(I/M)DR-NHR" wherein R" is alkyl of 3-10 carbons.

12. The compound of claims 1-9 wherein AA_{109}-AA_{110}-AA_{111}-AA_{112}-AA_{113}- is RIDRI, and Z_3 is NH_2.

13. The compound of claim 1 which is analog #122: MBP-4-APA-R-I-D-R-I-NH_2.

14. The compound of claim 1 which is selected from the group consisting of the compounds of Figure 4.

15. A composition useful as a natriuretic, diuretic and/or vasodilator comprising a therapeutically effective amount of the compound of claim 1 together with a pharmaceutically acceptable carrier.

16. A process for production of a peptide compound having natriuretic, diuretic and/or vasodilator activity in mammals, said peptide compound having the formula of the compound of claim 1, or the pharmacologically acceptable salts thereof, which process comprises the following steps:

a. preparing a protected peptide bonded to a solid resin carrier in a reaction mixture, wherein the peptide has an amino acid sequence as recited above;

b. removing the solid resin carrier from the peptide and deprotecting the peptide;

c. optionally modifying the peptide to add any desired organic substituent groups as recited above; and

d. isolating the peptide from any reaction mixture, and optionally, converting the polypeptide into an acid addition salt thereof.

FIG. 1

Acidic: Glu (E), Asp (D); Cysteic (Cya)

Non-Cyclic: Lys (K), Arg (R); Ornithine (Orn)

Basic:

Cyclic: His (H)

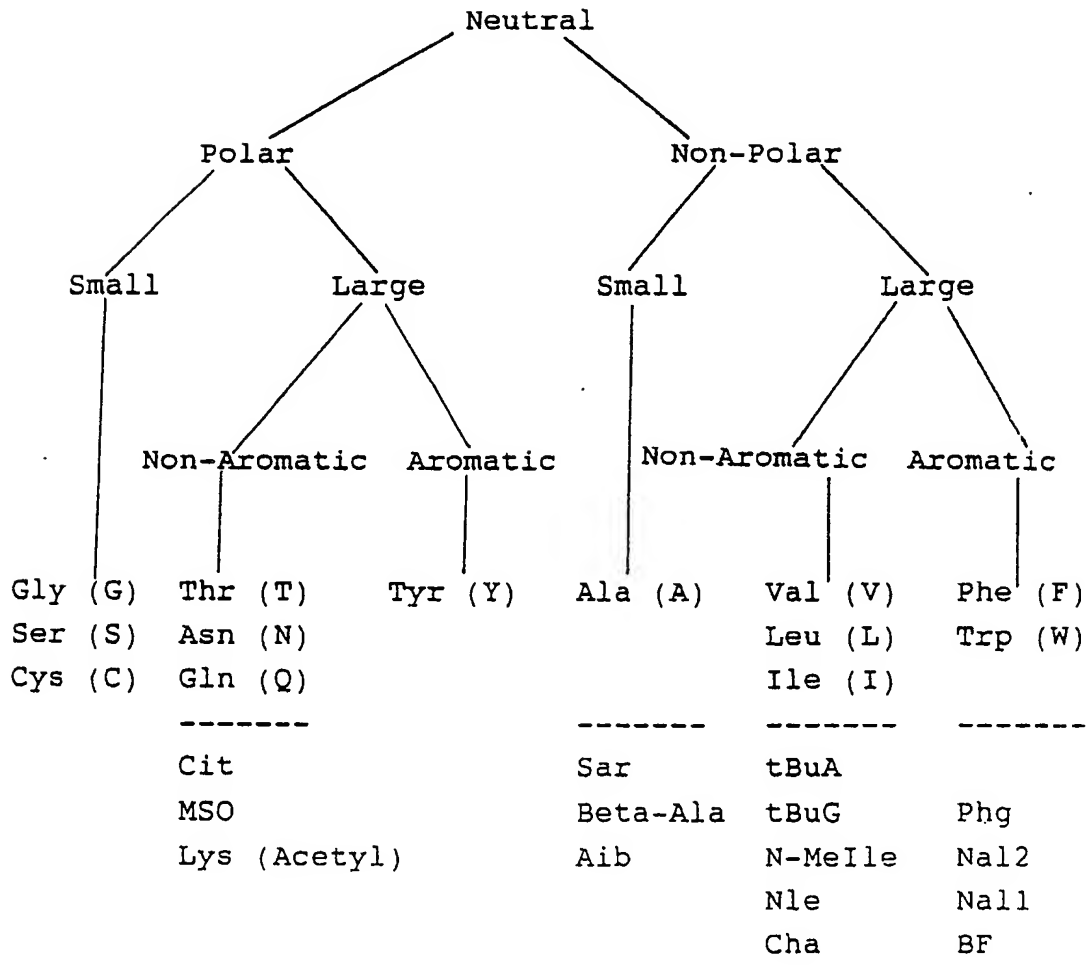
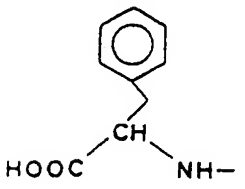
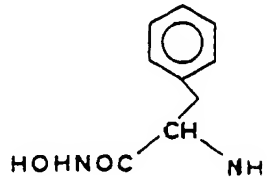


FIG. 2

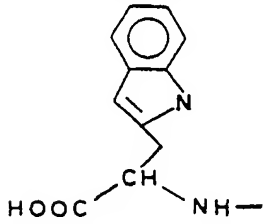
Embodiments of Z_1

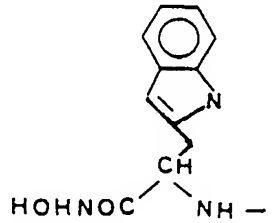
Z1 F is phenylalanyl; HAF is the hydroxamate thereof:



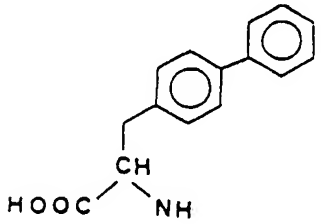


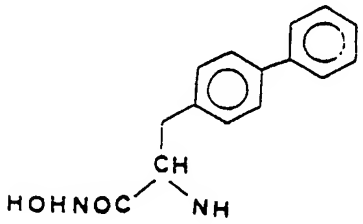
Z2 W is tryptophanyl; HAW is the hydroxamate thereof:



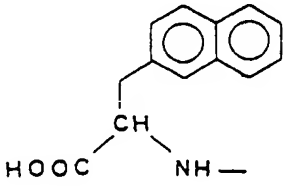


Z3 BF is p-biphenylalanyl; HABF is the hydroxamate thereof:





Z4 Nal2 is 3-(2'-naphthyl)alanyl; HANal2 is the hydroxamate thereof:



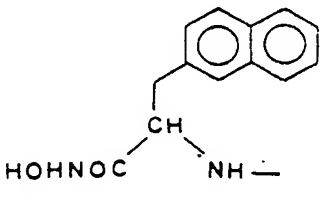
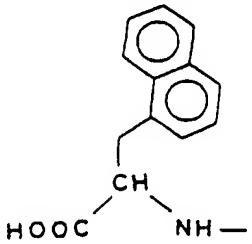
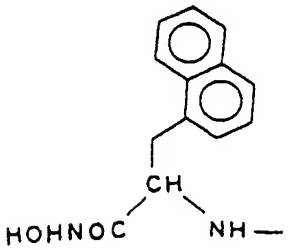


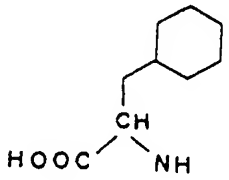
FIG. 2 (contd.)

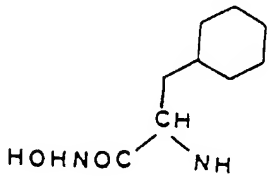
Z5 Nal1 is 3-(1'-naphthyl)alanyl; HANal1 is the hydroxamate thereof:



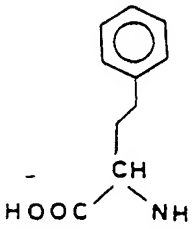


Z6 Cha is 3-(cyclohexyl)alanyl; HACha is the hydroxamate thereof:





Z7 homoF is homophenylalanyl; HAhomoF is the hydroxamate thereof:



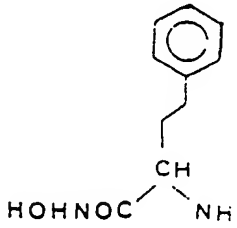
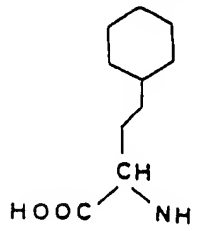
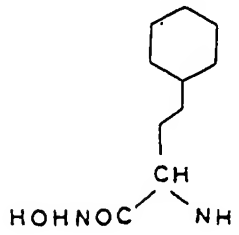


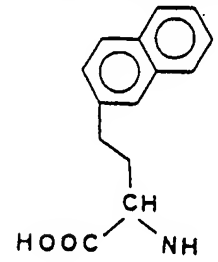
FIG. 2 (contd.)

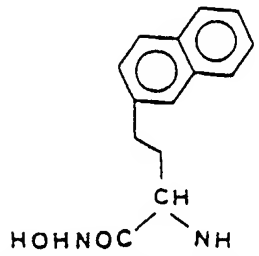
Z8 homoCha is 3-(cyclohexylmethyl)alanyl; HAhomoCha is the hydroxamate thereof:





Z9 homoNal2 is 3-(2'-naphthyl methyl)alanyl; HAhomoNal2 is the hydroxamate thereof:





Z10 X[N]F is derivatized phenylalanyl, wherein X is F homoF or G, or the hydroxamate thereof:

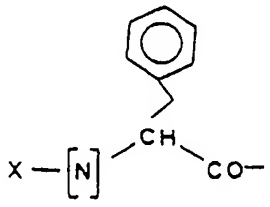
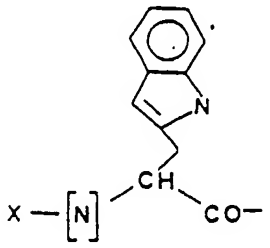
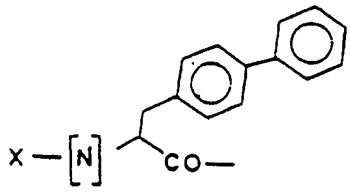


FIG. 2(contd.)

Z11 X[N]W is derivatized typtophanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z12 X[N]BF is derivatized p-biphenylalanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z13 X[N]Nal2 is derivatized beta-(2'-naphthyl)alanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:

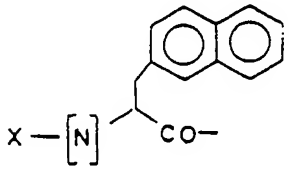
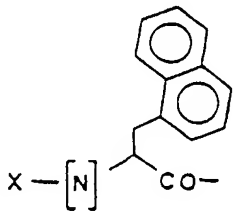
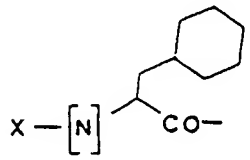


FIG. 2 (contd.)

Z14 X[N]Nall is derivatized 3-(1'-naphthyl)alanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z15 X[N]Cha is derivatized 3-(cyclohexyl)alanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z16 X[N]homoF is derivatized homophenylalanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:

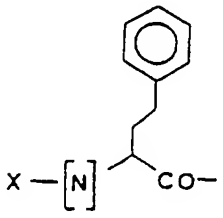
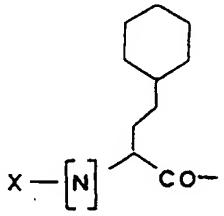
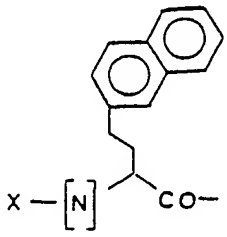


FIG. 2 (contd.)

Z17 X[N]homoCha is derivatized 3-(cyclohexylmethyl)alanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z18 X[N]Nal2 is derivatized 3-(2'-naphthylmethyl)alanyl, wherein X is F, homoF, or G, or the hydroxamate thereof:



Z19 phosphoryl-F is

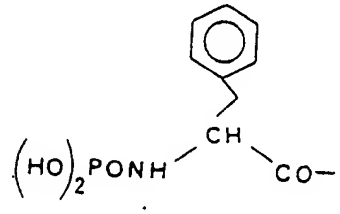
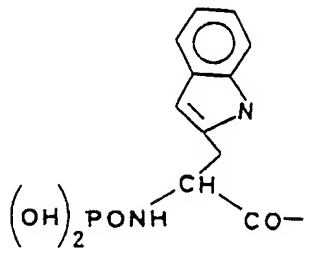
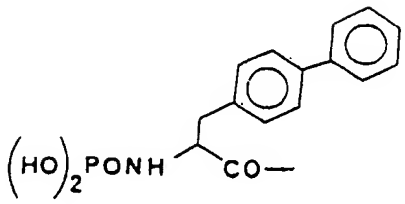


FIG. 2 (contd.)

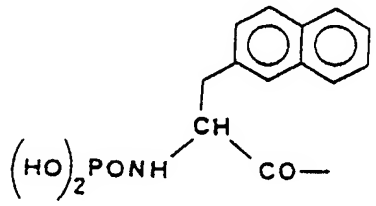
Z20 phosphoryl W is



Z21 phosphoryl BF is



Z22 phosphoryl Nal2 is



Z23 phosphoryl Nal1 is

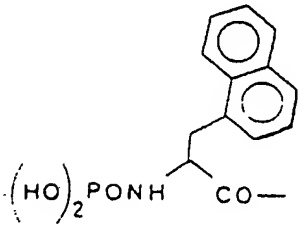
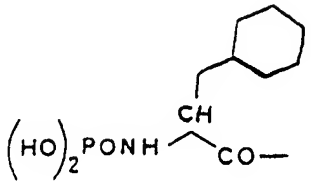
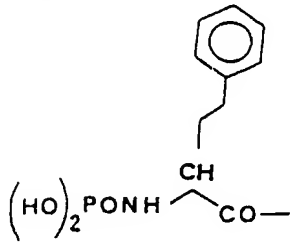


FIG. 2 (contd.)

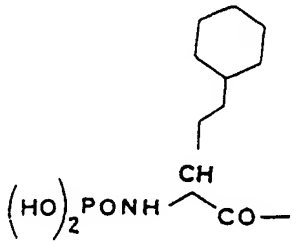
Z24 phosphoryl Cha is



Z25 phosphoryl homoF is



Z26 phosphoryl homoCha is



Z27 phosphoryl homoNal2 is

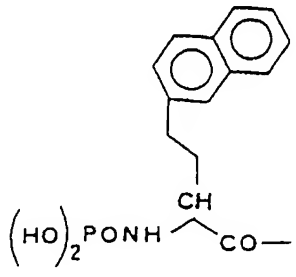
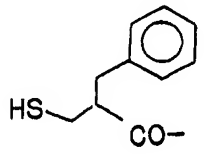
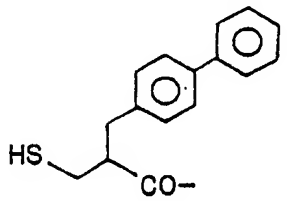


FIG. 2 (contd.)

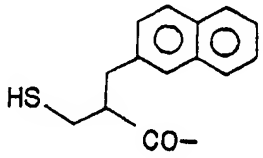
Z28 MBP is 3-mercapto-2-benzyl-propionyl;



Z29 MPBP is 3-mercapto-2-(p-biphenylmethyl)propionyl:



Z30 MNP2 is 3-mercapto-2-(2-'-naphthylmethyl)propionyl:



Z31 MNP1 is 3-mercapto-2-(1'-naphthylmethyl)propionyl:

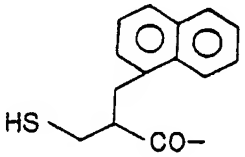
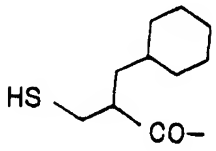
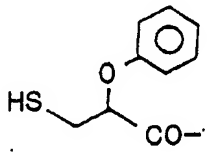


FIG. 2(contd.)

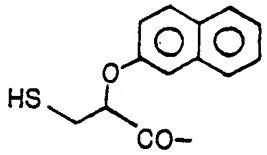
Z32 MCP is 3-mercapto-2-cyclohexylmethyl-propionyl:



Z33 MPOP is 3-mercapto-2-phenoxy-propionyl:



Z34 MNOP2 is 3-mercapto-2-(2'-naphthoxy)propionyl:



Z35 MIP3 is 3-mercapto-2-(3-indolemethyl)propionyl:

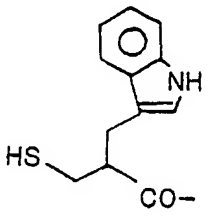
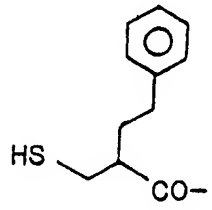
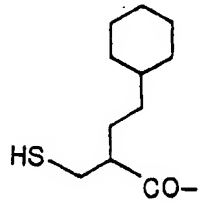


FIG. 2 (contd.)

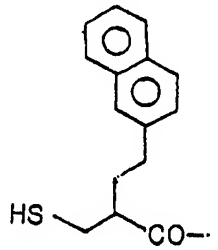
Z36 MPEP is 3-mercapto-2-phenylethyl-propionyl:



Z37 MCEP is 3-mercapto-2-cyclohexylethyl-propionyl:



Z38 MNEP2 is 3-mercapto-2-(2'-naphthylethyl)propionyl:



Z39 MBB is 4-mercapto-2-benzyl-butyryl:

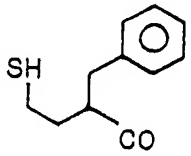
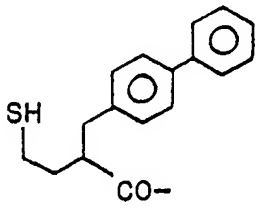
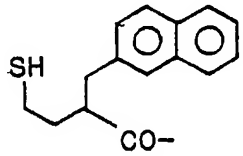


FIG. 2 (contd.)

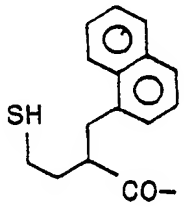
Z40 MPBB is 4-mercapto-2-(p-biphenylmethyl)butyryl:



Z41 MNB2 is 4-mercapto-2-(2'-naphthylmethyl)butyryl:



Z42 NMB1 is 4-mercapto-2-(1'-naphthylmethyl)butyryl:



Z43 MCB is 4-mercapto-2-cyclohexylmethyl-butyryl:

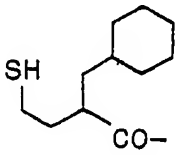
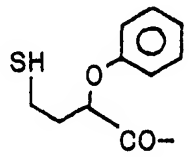
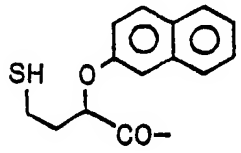


FIG. 2 (contd.)

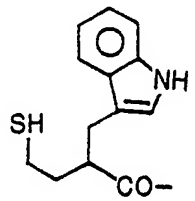
Z44 MPOB is 4-mercapto-2-phenoxy-butyryl:



Z45 MNOB2 is 4-mercapto-2-(2'-naphthoxy)butyryl:



Z46 MIB3 is 4-mercapto-2-(3-indolemethyl)butyryl:



Z47 MPEB is 4-mercapto-2-phenylethyl-butyryl:

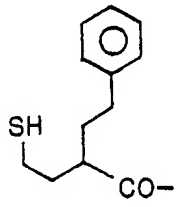
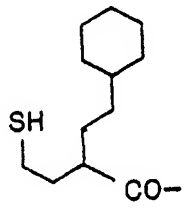
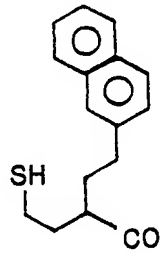


FIG. 2 (contd.)

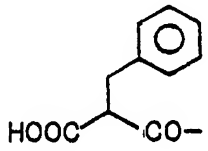
Z48 MCEB is 4-mercapto-2-cyclohexylmethyl-butyryl:



Z49 MNEB2 is 4-mercapto-2-(2'-naphthylethyl)butyryl:



Z50 BMAL is 2-benzylmalonyl:



Z51 PBMAL is 2-(p-biphenylmethyl)malonyl:

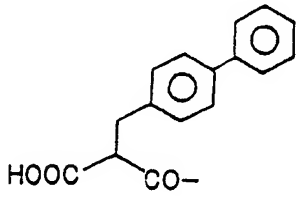
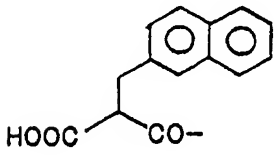
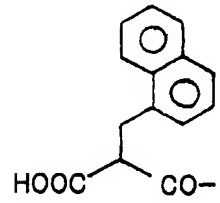


FIG. 2(contd.)

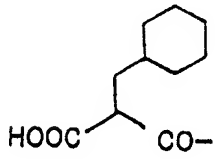
Z52 NMAL2 is 2-(2'-naphthylmethyl)malonyl:



Z53 NMAL1 is 2-(1'-naphthylmethyl)malonyl:



Z54 CMAL is 2-cyclohexylmethylmalonyl:



Z55 PMAL is 2-phenoxymalonyl:

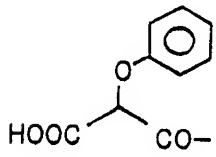
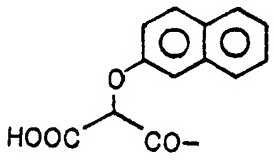
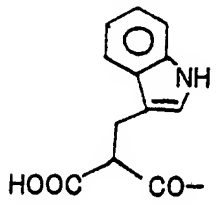


FIG. 2 (contd.)

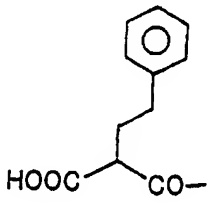
Z56 NOMAL2 is 2-(2'-naphthoxy)malonyl:



Z57 IMAL is 2-(3-indolemethyl)malonyl:



Z58 PEMAL is 2-phenylethylmalonyl:



Z59 CEMAL is 2-cyclohexylethylmalonyl:

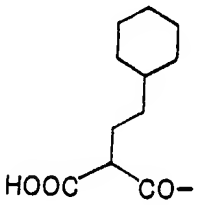
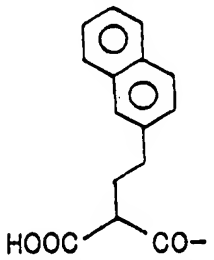
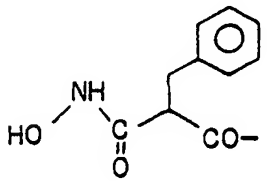


FIG. 2 (contd.)

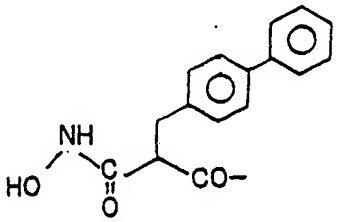
Z60 NEMAL is 2-(2'-naphthylethyl)malonyl:



Z61 BHAMAL is 2-benzyl-hydroxyamino-malonyl:



Z62 PBHAMAL is 2-(p-biphenylmethyl)-hydroxyamino-malonyl:



Z63 NHAMAL2 is 2-(2'-naphthylmethyl)-hydroxyamino-malonyl:

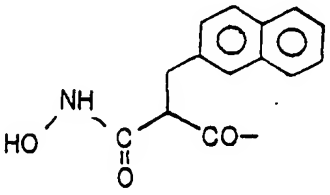
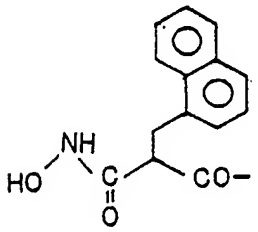
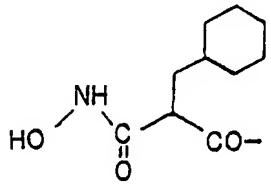


FIG. 2 (contd.)

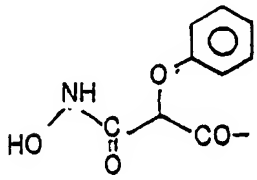
Z64 NHAMAL1 is 2-(1'-naphthylmethyl)-hydroxyamino-malonyl:



Z65 CHAMAL is 2-cyclohexylmethyl-hydroxyamino-malonyl:



Z66 PHAMAL is 2-phenoxy-hydroxyamino-malonyl:



Z67 NOHAMAL2 is 2-(2'-naphthoxy)-hydroxyamino-malonyl:

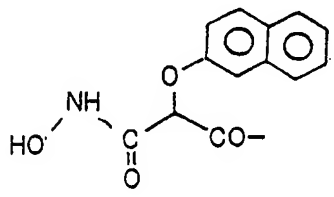
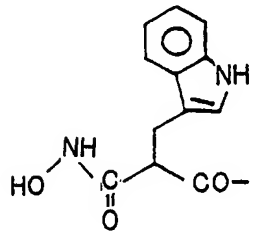
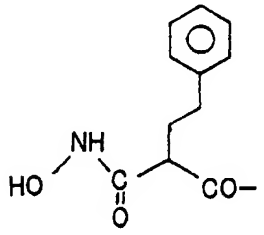


FIG. 2(contd.)

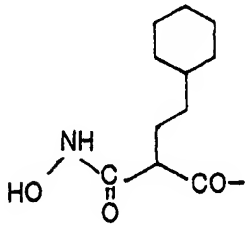
Z68 IHAMAL is 2-(3-indolemethyl)-hydroxyamino-malonyl:



Z69 PEHAMAL is 2-phenylethyl-hydroxyamino-malonyl:



Z70 CEHAMAL is 2-cyclohexylethyl-hydroxyamino-malonyl:



Z71 NEHAMAL is 2-(2'-naphthylethyl)-hydroxyamino-malonyl:

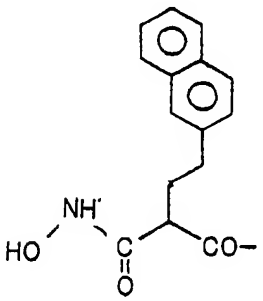
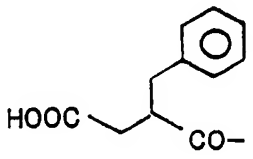
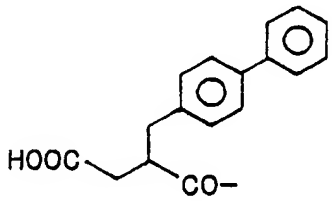


FIG. 2 (contd.)

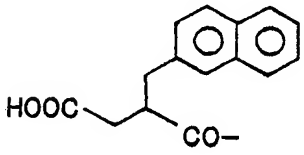
Z72 BSUC is 2-benzylsuccinoyl:



Z73 PBSUC is 2-(p-biphenylmethyl)succinoyl:



Z74 NSUC1 is 2-(2'-naphthylmethyl)succinoyl:



Z75 NSUC2 is 2-(1'-naphthylmethyl)succinoyl:

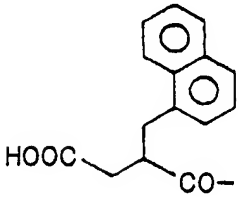
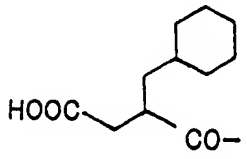
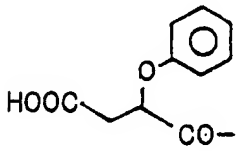


FIG. 2 (contd.)

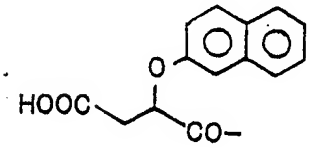
Z76 CSUC is 2-cyclohexylmethylsuccinoyl:



Z77 PSUC is 2-phenoxysuccinoyl:



Z78 NOSUC2 is 2-(2'-naphthoxy)succinoyl:



Z79 ISUC is 2-(3'-indolemethyl)succinoyl:

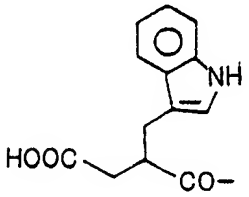
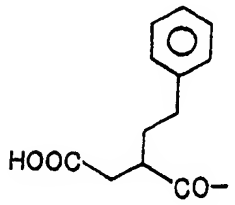
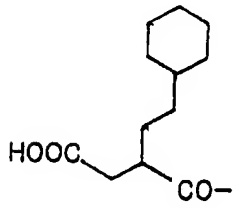


FIG. 2 (contd.)

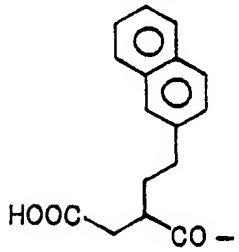
Z80 PESUC is 2-phenylethylsuccinoyl:



Z81 CESUC is 2-cyclohexylethylsuccinoyl:



Z82 NESUC is 2-(2'-naphthylethyl)succinoyl:



Z83 BHASUC is 2-benzyl-hydroxyamino-succinyl:

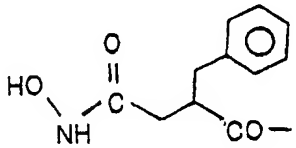
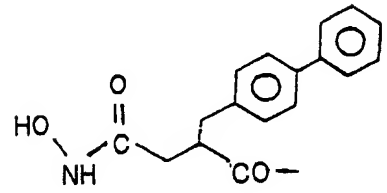
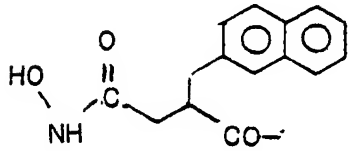


FIG. 2(contd.)

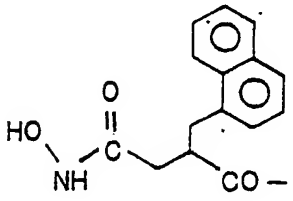
Z84 PBHASUC is 2-(p-biphenylmethyl)-hydroxyamino-succinyl:



Z85 NHASUC2 is 2-(2'-naphthylmethyl)-hydroxyamino-succinyl:



Z86 NHASUC1 is 2-(1'-naphthylmethyl)-hydroxyamino-succinyl:



Z87 CHASUC is 2-cyclohexylmethyl-hydroxyamino-succinyl:

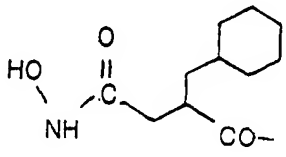
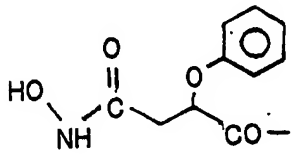
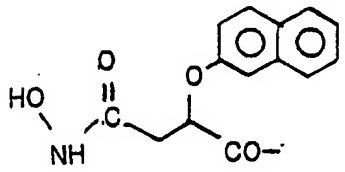


FIG. 2 (contd.)

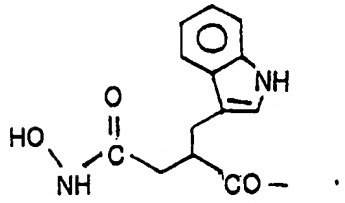
Z88 PHASUC is 2-phenoxy-hydroxyamino-succinyl:



Z89 NOHASUC2 is 2-(2'-naphthoxy)-hydroxyamino-succinyl:



Z90 IHASUC is 2-(3-indolemethyl)-hydroxyamino-succinyl:



Z91 PEHASUC is 2-phenylethyl-hydroxyamino-succinyl:

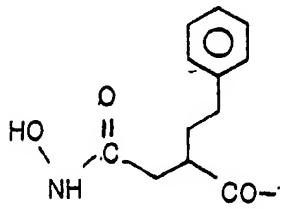
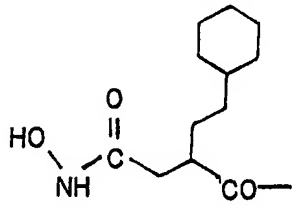


FIG. 2 (contd.)

Z92 CEHASUC is 2-cyclohexylethyl-hydroxyamino-succinyl:



Z93 NEHASUC is 2-(2'-naphthylethyl)-hydroxyamino-succinyl:

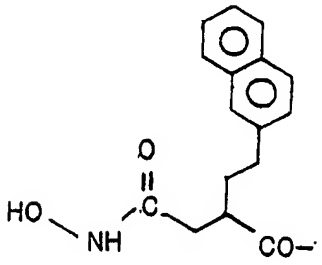
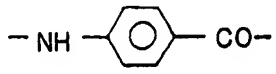


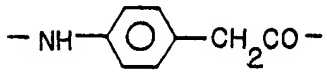
FIG. 3

Embodiments Z_2

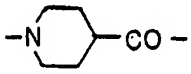
4-AB is 4-aminobenzoyl:



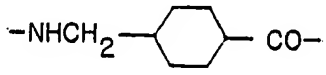
4-APA is 4-aminophenylacetyl:



4-PIP is 4-piperidine-carboxyl:



4-AMC is 4-aminomethylcyclohexoyl:



(trans)

FIG. 4

1	MBP-G-G-R-I-D-R-I-NH_2
2	MPBP-G-G-R-I-D-R-I-NH_2
3	MNP2-G-G-R-I-D-R-I-NH_2
4	MNP1-G-G-R-I-D-R-I-NH_2
5	MCP-G-G-R-I-D-R-I-NH_2
6	MPOP-G-G-R-I-D-R-I-NH_2
7	MNOP2-G-G-R-I-D-R-I-NH_2
8	MIP3-G-G-R-I-D-R-I-NH_2
9	MPEP-G-G-R-I-D-R-I-NH_2
10	MCEP-G-G-R-I-D-R-I-NH_2
11	MNEP2-G-G-R-I-D-R-I-NH_2
12	MBP-D-G-R-I-D-R-I-NH_2
13	MPBP-D-G-R-I-D-R-I-NH_2
14	MNP2-D-G-R-I-D-R-I-NH_2
15	MNP1-D-G-R-I-D-R-I-NH_2
16	MCP-D-G-R-I-D-R-I-NH_2
17	MPOP-D-G-R-I-D-R-I-NH_2
18	MNOP2-D-G-R-I-D-R-I-NH_2
19	MIP3-D-G-R-I-D-R-I-NH_2
20	MPEP-D-G-R-I-D-R-I-NH_2
21	MCEP-D-G-R-I-D-R-I-NH_2
22	MNEP2-D-G-R-I-D-R-I-NH_2
23	MBP-[D-Asp]-G-R-I-D-R-I-NH_2
24	MPBP-[D-Asp]-G-R-I-D-R-I-NH_2
25	MNP2-[D-Asp]-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

26	MNP1-[D-Asp]-G-R-I-D-R-I-NH_2
27	MCP-[D-Asp]-G-R-I-D-R-I-NH_2
28	MPOP-[D-Asp]-G-R-I-D-R-I-NH_2
29	MNOP2-[D-Asp]-G-R-I-D-R-I-NH_2
30	MIP3-[D-Asp]-G-R-I-D-R-I-NH_2
31	MPEP-[D-Asp]-G-R-I-D-R-I-NH_2
32	MCEP-[D-Asp]-G-R-I-D-R-I-NH_2
33	MNEP2-[D-Asp]-G-R-I-D-R-I-NH_2
34	MBP-[D-Ala]-G-R-I-D-R-I-NH_2
35	MPBP-[D-Ala]-G-R-I-D-R-I-NH_2
36	MNP2-[D-Ala]-G-R-I-D-R-I-NH_2
37	MNP1-[D-Ala]-G-R-I-D-R-I-NH_2
38	MCP-[D-Ala]-G-R-I-D-R-I-NH_2
39	MPOP-[D-Ala]-G-R-I-D-R-I-NH_2
40	MNOP2-[D-Ala]-G-R-I-D-R-I-NH_2
41	MIP3-[D-Ala]-G-R-I-D-R-I-NH_2
42	MPEP-[D-Ala]-G-R-I-D-R-I-NH_2
43	MCEP-[D-Ala]-G-R-I-D-R-I-NH_2
44	MNEP2-[D-Ala]-G-R-I-D-R-I-NH_2
45	MBP-[β-L-Asp]-G-R-I-D-R-I-NH_2
46	MPBP-[β-L-Asp]-G-R-I-D-R-I-NH_2
47	MNP2-[β-L-Asp]-G-R-I-D-R-I-NH_2
48	MNP1-[β-L-Asp]-G-R-I-D-R-I-NH_2
49	MCP-[β-L-Asp]-G-R-I-D-R-I-NH_2
50	MPOP-[β-L-Asp]-G-R-I-D-R-I-NH_2
51	MNOP2-[β-L-Asp]-G-R-I-D-R-I-NH_2
52	MIP3-[β-L-Asp]-G-R-I-D-R-I-NH_2

53 MPEP-[β-L-Asp]-G-R-I-D-R-I-NH_2

54 MCEP-[β-L-Asp]-G-R-I-D-R-I-NH_2

55 MNEP2-[β-L-Asp]-G-R-I-D-R-I-NH_2

56 MBP-[β-D-Asp]-G-R-I-D-R-I-NH_2

57 MPBP-[β-D-Asp]-G-R-I-D-R-I-NH_2

58 MNP2-[β-D-Asp]-G-R-I-D-R-I-NH_2

59 MNP1-[β-D-Asp]-G-R-I-D-R-I-NH_2

60 MCP-[β-D-Asp]-G-R-I-D-R-I-NH_2

61 MPOP-[β-D-Asp]-G-R-I-D-R-I-NH_2

62 MNOP2-[β-D-Asp]-G-R-I-D-R-I-NH_2

63 MIP3-[β-D-Asp]-G-R-I-D-R-I-NH_2

64 MPEP-[β-D-Asp]-G-R-I-D-R-I-NH_2

65 MCEP-[β-D-Asp]-G-R-I-D-R-I-NH_2

66 MNEP2-[β-D-Asp]-G-R-I-D-R-I-NH_2

67 MBP-[γ-D-Glu]-R-I-D-R-I-NH_2

68 MPBP-[γ-D-Glu]-R-I-D-R-I-NH_2

69 MNP2-[γ-D-Glu]-R-I-D-R-I-NH_2

70 MNP1-[γ-D-Glu]-R-I-D-R-I-NH_2

71 MCP-[γ-D-Glu]-R-I-D-R-I-NH_2

72 MPOP-[γ-D-Glu]-R-I-D-R-I-NH_2

73 MNOP2-[γ-D-Glu]-R-I-D-R-I-NH_2

74 MIP3-[γ-D-Glu]-R-I-D-R-I-NH_2

75 MPEP-[γ-D-Glu]-R-I-D-R-I-NH_2

76 MCEP-[γ-D-Glu]-R-I-D-R-I-NH_2

77 MNEP2-[γ-D-Glu]-R-I-D-R-I-NH_2

78 MBP-[γ-L-Glu]-R-I-D-R-I-NH_2

79 MPBP-[γ-L-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

FIG. 4 (contd.)

80 MNP2-[γ-L-Glu]-R-I-D-R-I-NH_2

81 MNP1-[γ-L-Glu]-R-I-D-R-I-NH_2

82 MCP-[γ-L-Glu]-R-I-D-R-I-NH_2

83 MPOP-[γ-L-Glu]-R-I-D-R-I-NH_2

84 MNOP2-[γ-L-Glu]-R-I-D-R-I-NH_2

85 MIP3-[γ-L-Glu]-R-I-D-R-I-NH_2

86 MPEP-[γ-L-Glu]-R-I-D-R-I-NH_2

87 MCEP-[γ-L-Glu]-R-I-D-R-I-NH_2

88 MNEP2-[γ-L-Glu]-R-I-D-R-I-NH_2

89 MBP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

90 MPBP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

91 MNP2-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

92 MNP1-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

93 MCP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

94 MPOP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

95 MNOP2-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

96 MIP3-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

97 MPEP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

98 MCEP-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

99 MNEP2-$NH(CH_2)_3CO$-R-I-D-R-I-NH_2

100 MBP-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

101 MPBP-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

102 MNP2-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

103 MNP1-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

104 MCP-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

105 MPOP-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

106 MNOP2-$NH(CH_2)_4CO$-R-I-D-R-I-NH_2

107	MIP3-NH$(CH_2)_4$CO-R-I-D-R-I-NH_2
108	MPEP-NH$(CH_2)_4$CO-R-I-D-R-I-NH_2
109	MCEP-NH$(CH_2)_4$CO-R-I-D-R-I-NH_2
110	MNEP2-NH$(CH_2)_4$CO-R-I-D-R-I-NH_2
111	MBP-4-PIP-R-I-D-R-I-NH_2
112	MPBP-4-PIP-R-I-D-R-I-NH_2
113	MNP2-4-PIP-R-I-D-R-I-NH_2
114	MNP1-4-PIP-R-I-D-R-I-NH_2
115	MCP-4-PIP-R-I-D-R-I-NH_2
116	MPOP-4-PIP-R-I-D-R-I-NH_2
117	MNOP2-4-PIP-R-I-D-R-I-NH_2
118	MIP3-4-PIP-R-I-D-R-I-NH_2
119	MPEP-4-PIP-R-I-D-R-I-NH_2
120	MCEP-4-PIP-R-I-D-R-I-NH_2
121	MNEP2-4-PIP-R-I-D-R-I-NH_2
122	MBP-4-APA-R-I-D-R-I-NH_2
123	MPBP-4-APA-R-I-D-R-I-NH_2
124	MNP2-4-APA-R-I-D-R-I-NH_2
125	MNP1-4-APA-R-I-D-R-I-NH_2
126	MCP-4-APA-R-I-D-R-I-NH_2
127	MPOP-4-APA-R-I-D-R-I-NH_2
128	MNOP2-4-APA-R-I-D-R-I-NH_2
129	MIP3-4-APA-R-I-D-R-I-NH_2
130	MPEP-4-APA-R-I-D-R-I-NH_2
131	MCEP-4-APA-R-I-D-R-I-NH_2
132	MNEP2-4-APA-R-I-D-R-I-NH_2
133	MBP-4-AB-R-I-D-R-I-NH_2

FIG. 4 (contd.)

FIG. 4 (contd.)

134	MPBP-4-AB-R-I-D-R-I-NH_2
135	MNP2-4-AB-R-I-D-R-I-NH_2
136	MNP1-4-AB-R-I-D-R-I-NH_2
137	MCP-4-AB-R-I-D-R-I-NH_2
138	MPOP-4-AB-R-I-D-R-I-NH_2
139	MNOP2-4-AB-R-I-D-R-I-NH_2
140	MIP3-4-AB-R-I-D-R-I-NH_2
141	MPEP-4-AB-R-I-D-R-I-NH_2
142	MCEP-4-AB-R-I-D-R-I-NH_2
143	MNEP2-4-AB-R-I-D-R-I-NH_2
144	MBP-4-AMC-R-I-D-R-I-NH_2
145	MPBP-4-AMC-R-I-D-R-I-NH_2
146	MNP2-4-AMC-R-I-D-R-I-NH_2
147	MNP1-4-AMC-R-I-D-R-I-NH_2
148	MCP-4-AMC-R-I-D-R-I-NH_2
149	MPOP-4-AMC-R-I-D-R-I-NH_2
150	MNOP2-4-AMC-R-I-D-R-I-NH_2
151	MIP3-4-AMC-R-I-D-R-I-NH_2
152	MPEP-4-AMC-R-I-D-R-I-NH_2
153	MCEP-4-AMC-R-I-D-R-I-NH_2
154	MNEP2-4-AMC-R-I-D-R-I-NH_2
155	MBP-G-G-K-I-D-R-I-NH_2
156	MPBP-G-G-K-I-D-R-I-NH_2
157	MNP2-G-G-K-I-D-R-I-NH_2
158	MNP1-G-G-K-I-D-R-I-NH_2
159	MCP-G-G-K-I-D-R-I-NH_2
160	MPOP-G-G-K-I-D-R-I-NH_2

161 MNOP2-G-G-K-I-D-R-I-NH_2

162 MIP3-G-G-K-I-D-R-I-NH_2

163 MPEP-G-G-K-I-D-R-I-NH_2

164 MCEP-G-G-K-I-D-R-I-NH_2

165 MNEP2-G-G-K-I-D-R-I-NH_2

166 MBP-4-APA-K-I-D-R-I-NH_2

167 MPBP-4-APA-K-I-D-R-I-NH_2

168 MNP2-4-APA-K-I-D-R-I-NH_2

169 MNP1-4-APA-K-I-D-R-I-NH_2

170 MCP-4-APA-K-I-D-R-I-NH_2

171 MPOP-4-APA-K-I-D-R-I-NH_2

172 MNOP2-4-APA-K-I-D-R-I-NH_2

173 MIP3-4-APA-K-I-D-R-I-NH_2

174 MPEP-4-APA-K-I-D-R-I-NH_2

175 MCEP-4-APA-K-I-D-R-I-NH_2

176 MNEP2-4-APA-K-I-D-R-I-NH_2

177 MBP-D-G-K-I-D-R-I-NH_2

178 MPBP-D-G-K-I-D-R-I-NH_2

179 MNP2-D-G-K-I-D-R-I-NH_2

180 MNP1-D-G-K-I-D-R-I-NH_2

181 MCP-D-G-K-I-D-R-I-NH_2

182 MPOP-D-G-K-I-D-R-I-NH_2

183 MNOP2-D-G-K-I-D-R-I-NH_2

184 MIP3-D-G-K-I-D-R-I-NH_2

185 MPEP-D-G-K-I-D-R-I-NH_2

186 MCEP-D-G-K-I-D-R-I-NH_2

187 MNEP2-D-G-K-I-D-R-I-NH_2

FIG. 4 (contd.)

FIG. 4 (contd.)

188	MBP-[D-Asp]-G-K-I-D-R-I-NH_2
189	MPBP-[D-Asp]-G-K-I-D-R-I-NH_2
190	MNP2-[D-Asp]-G-K-I-D-R-I-NH_2
191	MNP1-[D-Asp]-G-K-I-D-R-I-NH_2
192	MCP-[D-Asp]-G-K-I-D-R-I-NH_2
193	MPOP-[D-Asp]-G-K-I-D-R-I-NH_2
194	MNOP2-[D-Asp]-G-K-I-D-R-I-NH_2
195	MIP3-[D-Asp]-G-K-I-D-R-I-NH_2
196	MPEP-[D-Asp]-G-K-I-D-R-I-NH_2
197	MCEP-[D-Asp]-G-K-I-D-R-I-NH_2
198	MNEP2-[D-Asp]-G-K-I-D-R-I-NH_2
199	MBP-[γ-L-Glu]-K-I-D-R-I-NH_2
200	MPBP-[γ-L-Glu]-K-I-D-R-I-NH_2
201	MNP2-[γ-L-Glu]-K-I-D-R-I-NH_2
202	MNP1-[γ-L-Glu]-K-I-D-R-I-NH_2
203	MCP-[γ-L-Glu]-K-I-D-R-I-NH_2
204	MPOP-[γ-L-Glu]-K-I-D-R-I-NH_2
205	MNOP2-[γ-L-Glu]-K-I-D-R-I-NH_2
206	MIP3-[γ-L-Glu]-K-I-D-R-I-NH_2
207	MPEP-[γ-L-Glu]-K-I-D-R-I-NH_2
208	MCEP-[γ-L-Glu]-K-I-D-R-I-NH_2
209	MNEP-[γ-L-Glu]-K-I-D-R-I-NH_2
210	MBP-[γ-D-Glu]-K-I-D-R-I-NH_2
211	MPBP-[γ-D-Glu]-K-I-D-R-I-NH_2
212	MNP2-[γ-D-Glu]-K-I-D-R-I-NH_2
213	MNP1-[γ-D-Glu]-K-I-D-R-I-NH_2
214	MCP-[γ-D-Glu]-K-I-D-R-I-NH_2

FIG. 4 (contd.)

215 MPOP-[γ-D-Glu]-K-I-D-R-I-NH_2

216 MNOP2-[γ-D-Glu]-K-I-D-R-I-NH_2

217 MIP3-[γ-D-Glu]-K-I-D-R-I-NH_2

218 MPEP-[γ-D-Glu]-K-I-D-R-I-NH_2

219 MCEP-[γ-D-Glu]-K-I-D-R-I-NH_2

220 MNEP2-[γ-D-Glu]-K-I-D-R-I-NH_2

221 MBP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

222 MPBP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

223 MNP2-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

224 MNP1-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

225 MCP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

226 MPOP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

227 MNOP2-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

228 MIP3-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

229 MPEP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

230 MCEP-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

231 MNEP2-G-G-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

232 MBP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

233 MPBP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

234 MNP2-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

235 MNP1-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

236 MCP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

237 MPOP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

238 MNOP2-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

239 MIP3-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

240 MPEP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

241 MCEP-4-APA-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

FIG. 4 (contd.)

242 MNEP2-4-APA-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

243 MBP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

244 MPBP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

245 MNP2-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

246 MNP1-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

247 MCP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

248 MPOP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

249 MNOP2-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

250 MIP3-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

251 MPEP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

252 MCEP-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

253 MNEP2-[D-Asp]-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

254 MBP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

255 MPBP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

256 MNP2-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

257 MNP1-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

258 MCP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

259 MPOP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

260 MNOP2-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

261 MIP3-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

262 MPEP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

263 MCEP-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

264 MNEP2-D-G-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

265 MBP-[γ-L-Glu]-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

266 MPBP-[γ-L-Glu]-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

267 MNP2-[γ-L-Glu]-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

268 MNP1-[γ-L-Glu]-R-I-D-R-NHCH$_2$CH(CH$_3$)CH$_2$CH$_3$

269 MCP-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

270 MPOP-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

271 MNOP2-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

272 MIP3-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

273 MPEP-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

274 MCEP-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

275 MNEP2-[γ-L-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

276 MBP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

277 MPBP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

278 MNP2-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

279 MNP1-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

280 MCP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

281 MPOP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

282 MNOP2-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

283 MIP3-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

284 MPEP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

285 MCEP-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

286 MNEP2-[γ-D-Glu]-R-I-D-R-$NHCH_2CH(CH_3)CH_2CH_3$

287 MBB-G-G-R-I-D-R-I-NH_2

288 MPBB-G-G-R-I-D-R-I-NH_2

289 MNB2-G-G-R-I-D-R-I-NH_2

290 MNB1-G-G-R-I-D-R-I-NH_2

291 MCB-G-G-R-I-D-R-I-NH_2

292 MPOB-G-G-R-I-D-R-I-NH_2

293 MNOB2-G-G-R-I-D-R-I-NH_2

294 MIB3-G-G-R-I-D-R-I-NH_2

295 MPEB-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

296 MCEB-G-G-R-I-D-R-I-NH_2

297 MNEB2-G-G-R-I-D-R-I-NH_2

298 MBB-4-APA-R-I-D-R-I-NH_2

299 MPBB-4-APA-R-I-D-R-I-NH_2

300 MNB2-4-APA-R-I-D-R-I-NH_2

301 MNB1-4-APA-R-I-D-R-I-NH_2

302 MCB-4-APA-R-I-D-R-I-NH_2

303 MPOB-4-APA-R-I-D-R-I-NH_2

304 MNOB2-4-APA-R-I-D-R-I-NH_2

305 MIB3-4-APA-R-I-D-R-I-NH_2

306 MPEB-4-APA-R-I-D-R-I-NH_2

307 MCEB-4-APA-R-I-D-R-I-NH_2

308 MNEB2-4-APA-R-I-D-R-I-NH_2

309 MBB-4-AB-R-I-D-R-I-NH_2

310 MPBB-4-AB-R-I-D-R-I-NH_2

311 MNB2-4-AB-R-I-D-R-I-NH_2

312 MNB1-4-AB-R-I-D-R-I-NH_2

313 MCB-4-AB-R-I-D-R-I-NH_2

314 MPOB-4-AB-R-I-D-R-I-NH_2

315 MNOB2-4-AB-R-I-D-R-I-NH_2

316 MIB3-4-AB-R-I-D-R-I-NH_2

317 MPEB-4-AB-R-I-D-R-I-NH_2

318 MCEB-4-AB-R-I-D-R-I-NH_2

319 MNEB2-4-AB-R-I-D-R-I-NH_2

320 MBB-D-G-R-I-D-R-I-NH_2

321 MPBB-D-G-R-I-D-R-I-NH_2

322 MNB2-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

323 MNB1-D-G-R-I-D-R-I-NH_2

324 MCB-D-G-R-I-D-R-I-NH_2

325 MPOB-D-G-R-I-D-R-I-NH_2

326 MNOB2-D-G-R-I-D-R-I-NH_2

327 MIB3-D-G-R-I-D-R-I-NH_2

328 MPEB-D-G-R-I-D-R-I-NH_2

329 MCEB-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

330 MNEB2-D-G-R-I-D-R-I-NH_2

331 MBB-[D-Asp]-G-R-I-D-R-I-NH_2

332 MPBB-[D-Asp]-G-R-I-D-R-I-NH_2

333 MNB2-[D-Asp]-G-R-I-D-R-I-NH_2

334 MNB1-[D-Asp]-G-R-I-D-R-I-NH_2

335 MCB-[D-Asp]-G-R-I-D-R-I-NH_2

336 MPOB-[D-Asp]-G-R-I-D-R-I-NH_2

337 MNOB2-[D-Asp]-G-R-I-D-R-I-NH_2

338 MIB3-[D-Asp]-G-R-I-D-R-I-NH_2

339 MPEB-[D-Asp]-G-R-I-D-R-I-NH_2

340 MCEB-[D-Asp]-G-R-I-D-R-I-NH_2

341 MNEB2-[D-Asp]-G-R-I-D-R-I-NH_2

342 MBB-[γ-L-Glu]-R-I-D-R-I-NH_2

343 MPBB-[γ-L-Glu]-R-I-D-R-I-NH_2

344 MNB2-[γ-L-Glu]-R-I-D-R-I-NH_2

345 MNB1-[γ-L-Glu]-R-I-D-R-I-NH_2

346 MCB-[γ-L-Glu]-R-I-D-R-I-NH_2

347 MPOB-[γ-L-Glu]-R-I-D-R-I-NH_2

348 MNOB2-[γ-L-Glu]-R-I-D-R-I-NH_2

349 MIB3-[γ-L-Glu]-R-I-D-R-I-NH_2

350 MPEB-[γ-L-Glu]-R-I-D-R-I-NH_2

351 MCEB-[γ-L-Glu]-R-I-D-R-I-NH_2

352 MNEB2-[γ-L-Glu]-R-I-D-R-I-NH_2

353 MBB-[γ-D-Glu]-R-I-D-R-I-NH_2

354 MPBB-[γ-D-Glu]-R-I-D-R-I-NH_2

355 MNB2-[γ-D-Glu]-R-I-D-R-I-NH_2

356 MNB1-[γ-D-Glu]-R-I-D-R-I-NH_2

357 MCB-[γ-D-Glu]-R-I-D-R-I-NH_2

358 MPOB-[γ-D-Glu]-R-I-D-R-I-NH_2

359 MNOB2-[γ-D-Glu]-R-I-D-R-I-NH_2

360 MIB3-[γ-D-Glu]-R-I-D-R-I-NH_2

361 MPEB-[γ-D-Glu]-R-I-D-R-I-NH_2

362 MCEB-[γ-D-Glu]-R-I-D-R-I-NH_2

363 MNEB2-[γ-D-Glu]-R-I-D-R-I-NH_2

364 F[N]G-G-R-I-D-R-I-NH_2

365 BF[N]G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

366 Nal2[N]G-G-R-I-D-R-I-NH_2

367 Nal1[N]G-G-R-I-D-R-I-NH_2

368 Cha[N]G-G-R-I-D-R-I-NH_2

369 W[N]G-G-R-I-D-R-I-NH_2

370 homoF[N]G-G-R-I-D-R-I-NH_2

371 homoCha[N]G-G-R-I-D-R-I-NH_2

372 homoNal2[N]G-G-R-I-D-R-I-NH_2

373 F[N]4-APA-R-I-D-R-I-NH_2

374 BF[N]4-APA-R-I-D-R-I-NH_2

375 Nal2[N]4-APA-R-I-D-R-I-NH_2

376 Nal1[N]4-APA-R-I-D-R-I-NH_2

377 Cha[N]4-APA-R-I-D-R-I-NH_2

378 W[N]4-APA-R-I-D-R-I-NH_2

379 homoF[N]4-APA-R-I-D-R-I-NH_2

380 homoCha[N]4-APA-R-I-D-R-I-NH_2

381 homoNal2[N]4-APA-R-I-D-R-I-NH_2

382 F[N]4-AB-R-I-D-R-I-NH_2

383 BF[N]4-AB-R-I-D-R-I-NH_2

384 Nal2[N]4-AB-R-I-D-R-I-NH_2

385 Nal1[N]4-AB-R-I-D-R-I-NH_2

386 Cha[N]4-AB-R-I-D-R-I-NH_2

387 W[N]4-AB-R-I-D-R-I-NH_2

388 homoF[N]4-AB-R-I-D-R-I-NH_2

389 homoCha[N]4-AB-R-I-D-R-I-NH_2

390 homoNal2[N]4-AB-R-I-D-R-I-NH_2

391 F[N]D-G-R-I-D-R-I-NH_2

392 BF[N]D-G-R-I-D-R-I-NH_2

393 Nal2[N]D-G-R-I-D-R-I-NH_2

394 Nal1[N]D-G-R-I-D-R-I-NH_2

395 Cha[N]D-G-R-I-D-R-I-NH_2

396 W[N]D-G-R-I-D-R-I-NH_2

397 homoF[N]D-G-R-I-D-R-I-NH_2

398 homoCha[N]D-G-R-I-D-R-I-NH_2

399 homoNal2[N]D-G-R-I-D-R-I-NH_2

400 F[N][D-Asp]-G-R-I-D-R-I-NH_2

401 BF[N][D-Asp]-G-R-I-D-R-I-NH_2

402 Nal2[N][D-Asp]-G-R-I-D-R-I-NH_2

403 Nal1[N][D-Asp]-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

404 Cha[N][D-Asp]-G-R-I-D-R-I-NH_2

405 W[N][D-Asp]-G-R-I-D-R-I-NH_2

406 homoF[N][D-Asp]-G-R-I-D-R-I-NH_2

407 homoCha[N][D-Asp]-G-R-I-I-R-I-NH_2

408 homoNal2[N][D-Asp]-G-R-I-D-R-I-NH_2

409 F[N][γ-L-Glu]-R-I-D-R-I-NH_2

410 BF[N][γ-L-Glu]-R-I-D-R-I-NH_2

411 Nal2[N][γ-L-Glu]-R-I-D-R-I-NH_2

412 Nal1[N][γ-L-Glu]-R-I-D-R-I-NH_2

413 Cha[N][γ-L-Glu]-R-I-D-R-I-NH_2

414 W[N][γ-L-Glu]-R-I-D-R-I-NH_2

415 homoF[N][γ-L-Glu]-R-I-D-R-I-NH_2

416 homoCha[N][γ-L-Glu]-R-I-D-R-I-NH_2

417 homoNal2[N][γ-L-Glu]-R-I-D-R-I-NH_2

418 F[N][γ-D-Glu]-R-I-D-R-I-NH_2

419 BF[N][γ-D-Glu]-R-I-D-R-I-NH_2

420 Nal2[N][γ-D-Glu]-R-I-D-R-I-NH_2

421 Nal1[N][γ-D-Glu]-R-I-D-R-I-NH_2

422 Cha[N][γ-D-Glu]-R-I-D-R-I-NH_2

423 W[N][γ-D-Glu]-R-I-D-R-I-NH_2

424 homoF[N][γ-D-Glu]-R-I-D-R-I-NH_2

425 homoCha[N][γ-D-Glu]-R-I-D-R-I-NH_2

426 homoNal2[N][γ-D-Glu]-R-I-D-R-I-NH_2

427 F[N][β-Ala]-G-R-I-D-R-I-NH_2

428 BF[N][β-Ala]-G-R-I-D-R-I-NH_2

429 Nal2[N][β-Ala]-G-R-I-D-R-I-NH_2

430 Nal1[N][β-Ala]-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

431 Cha[N][β-Ala]-G-R-I-D-R-I-NH_2

432 W[N][β-Ala]-G-R-I-D-R-I-NH_2

433 homoF[N][β-Ala]-G-R-I-D-R-I-NH_2

434 homoCha[N][β-Ala]-G-R-I-D-R-I-NH_2

435 homoNal2[N][β-Ala]-G-R-I-D-R-I-NH_2

436 F[N]F-G-G-R-I-D-R-I-NH_2

437 F[N]BF-G-G-R-I-D-R-I-NH_2

438 F[N]Nal2-G-G-R-I-D-R-I-NH_2

439 F[N]Nal1-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

440 F[N]Cha-G-G-R-I-D-R-I-NH_2

441 F[N]W-G-G-R-I-D-R-I-NH_2

442 F[N]homoF-G-G-R-I-D-R-I-NH_2

443 F[N]homoCha-G-G-R-I-D-R-I-NH_2

444 F[N]homoNal2-G-G-R-I-D-R-I-NH_2

445 F[N]F-4-APA-R-I-D-R-I-NH_2

446 F[N]BF-4-APA-R-I-D-R-I-NH_2

447 F[N]Nal2-4-APA-R-I-D-R-I-NH_2

448 F[N]Nal1-4-APA-R-I-D-R-I-NH_2

449 F[N]Cha-4-APA-R-I-D-R-I-NH_2

450 F[N]W-4-APA-R-I-D-R-I-NH_2

451 F[N]homoF-4-APA-R-I-D-R-I-NH_2

452 F[N]homoCha-4-APA-R-I-D-R-I-NH_2

453 F[N]homoNal2-4-APA-R-I-D-R-I-NH_2

454 F[N]F-4-AB-R-I-D-R-I-NH_2

455 F[N]BF-4-AB-R-I-D-R-I-NH_2

456 F[N]Nal2-4-AB-R-I-D-R-I-NH_2

457 F[N]Nal1-4-AB-R-I-D-R-I-NH_2

458 F[N]Cha-4-AB-R-I-D-R-I-NH_2

459 F[N]W-4-AB-R-I-D-R-I-NH_2

460 F[N]homoF-4-AB-R-I-D-R-I-NH_2

461 F[N]homoCha-4-AB-R-I-D-R-I-NH_2

462 F[N]homoNal2-4-AB-R-I-D-R-I-NH_2

463 F[N]F-D-G-R-I-D-R-I-NH_2

464 F[N]BF-D-G-R-I-D-R-I-NH_2

465 F[N]Nal2-D-G-R-I-D-R-I-NH_2

466 F[N]Nal1-D-G-R-I-D-R-I-NH_2

467 F[N]Cha-D-G-R-I-D-R-I-NH_2

468 F[N]W-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

469 F[N]homoF-D-G-R-I-D-R-I-NH_2

470 F[N]homoCha-D-G-R-I-D-R-I-NH_2

471 F[N]homoNal2-D-G-R-I-D-R-I-NH_2

472 F[N]F-[D-Asp]-G-R-I-D-R-I-NH_2

473 F[N]BF-[D-Asp]-G-R-I-D-R-I-NH_2

474 F[N]Nal2-[D-Asp]-G-R-I-D-R-I-NH_2

475 F[N]Nal1-[D-Asp]-G-R-I-D-R-I-NH_2

476 F[N]Cha-[D-Asp]-G-R-I-D-R-I-NH_2

477 F[N]W-[D-Asp]-G-R-I-D-R-I-NH_2

478 F[N]homoF-[D-Asp]-G-R-I-D-R-I-NH_2

479 F[N]homoCha-[D-Asp]-G-R-I-D-R-I-NH_2

480 F[N]homoNal2-[D-Asp]-G-R-I-D-R-I-NH_2

481 F[N]F-[γ-L-Glu]-R-I-D-R-I-NH_2

482 F[N]BF-[γ-L-Glu]-R-I-D-R-I-NH_2

483 F[N]Nal2-[γ-L-Glu]-R-I-D-R-I-NH_2

484 F[N]Nal1-[γ-L-Glu]-R-I-D-R-I-NH_2

485 F[N]Cha-[γ-L-Glu]-R-I-D-R-I-NH_2

486 F[N]W-[γ-L-Glu]-R-I-D-R-I-NH_2

487 F[N]homoF-[γ-L-Glu]-R-I-D-R-I-NH_2

488 F[N]homoCha-[γ-L-Glu]-R-I-D-R-I-NH_2

489 F[N]homoNal2-[γ-L-Glu]-R-I-D-R-I-NH_2

490 F[N]F-[γ-D-Glu]-R-I-D-R-I-NH_2

491 F[N]BF-[γ-D-Glu]-R-I-D-R-I-NH_2

492 F[N]Nal2-[γ-D-Glu]-R-I-D-R-I-NH_2

493 F[N]Nal1-[γ-D-Glu]-R-I-D-R-I-NH_2

494 F[N]Cha-[γ-D-Glu]-R-I-D-R-I-NH_2

495 F[N]W-[γ-D-Glu]-R-I-D-R-I-NH_2

496 F[N]homoF-[γ-D-Glu]-R-I-D-R-I-NH_2

497 F[N]homoCha-[γ-D-Glu]-R-I-D-R-I-NH_2

498 F[N]homoNal2-[γ-D-Glu]-R-I-D-R-I-NH_2

499 homoF[N]F-G-G-R-I-D-R-I-NH_2

500 homoF[N]BF-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

501 homoF[N]Nal2-G-G-R-I-D-R-I-NH_2

502 homoF[N]Nal1-G-G-R-I-D-R-I-NH_2

503 homoF[N]Cha-G-G-R-I-D-R-I-NH_2

504 homoF[N]W-G-G-R-I-D-R-I-NH_2

505 homoF[N]homoF-G-G-R-I-D-R-I-NH_2

506 homoF[N]homoCha-G-G-R-I-D-R-I-NH_2

507 homoF[N]homoNal2-G-G-R-I-D-R-I-NH_2

508 homoF[N]F-4-APA-R-I-D-R-I-NH_2

509 homoF[N]BF-4-APA-R-I-D-R-I-NH_2

510 homoF[N]Nal2-4-APA-R-I-D-R-I-NH_2

511 homoF[N]Nal1-4-APA-R-I-D-R-I-NH_2

512 homoF[N]Cha-4-APA-R-I-D-R-I-NH_2

513 homoF[N]W-4-APA-R-I-D-R-I-NH_2

514 homoF[N]homoF-4-APA-R-I-D-R-I-NH_2

515 homoF[N]homoCha-4-APA-R-I-D-R-I-NH_2

516 homoF[N]homoNal2-4-APA-R-I-D-R-I-NH_2

517 homoF[N]F-4-AB-R-I-D-R-I-NH_2

518 homoF[N]BF-4-AB-R-I-D-R-I-NH_2

519 homoF[N]Nal2-4-AB-R-I-D-R-I-NH_2

520 homoF[N]Nal1-4-AB-R-I-D-R-I-NH_2

521 homoF[N]Cha-4-AB-R-I-D-R-I-NH_2

522 homoF[N]W-4-AB-R-I-D-R-I-NH_2

523 homoF[N]homoF-4-AB-R-I-D-R-I-NH_2

524 homoF[N]homoCha-4-AB-R-I-D-R-I-NH_2

525 homoF[N]homoNal2-4-AB-R-I-D-R-I-NH_2

FIG. 4 (contd.)

527 homoF[N]BF-D-G-R-I-D-R-I-NH_2

528 homoF[N]Nal2-D-G-R-I-D-R-I-NH_2

529 homoF[N]Nal1-D-G-R-I-D-R-I-NH_2

530 homoF[N]Cha-D-G-R-I-D-R-I-NH_2

531 homoF[N]W-D-G-R-I-D-R-I-NH_2

532 homoF[N]homoF-D-G-R-I-D-R-I-NH_2

533 homoF[N]homoCha-D-G-R-I-D-R-I-NH_2

534 homoF[N]homoNal2-D-G-R-I-D-R-I-NH_2

536 homoF[N]BF-[D-Asp]-G-R-I-D-R-I-NH_2

537 homoF[N]Nal2-[D-Asp]-G-R-I-D-R-I-NH_2

538 homoF[N]Nal1-[D-Asp]-G-R-I-D-R-I-NH_2

539 homoF[N]Cha-[D-Asp]-G-R-I-D-R-I-NH_2

540 homoF[N]W-[D-Asp]-G-R-I-D-R-I-NH_2

541 homoF[N]homoF-[D-Asp]-G-R-I-D-R-I-NH_2

542 homoF[N]homoCha-[D-Asp]-G-R-I-D-R-I-NH_2

543 homoF[N]homoNal2-[D-Asp]-G-R-I-D-R-I-NH_2

544 homoF[N]F-[γ-L-Glu]-R-I-D-R-I-NH_2

545 homoF[N]BF-[γ-L-Glu]-R-I-D-R-I-NH_2

546 homoF[N]Nal2-[γ-L-Glu]-R-I-D-R-I-NH_2

547 homoF[N]Nal1-[γ-L-Glu]-R-I-D-R-I-NH_2

548 homoF[N]Cha-[γ-L-Glu]-R-I-D-R-I-NH_2

549 homoF[N]W-[γ-L-Glu]-R-I-D-R-I-NH_2

550 homoF[N]homoF-[γ-L-Glu]-R-I-D-R-I-NH_2

551 homoF[N]homoCha-[γ-L-Glu]-R-I-D-R-I-NH_2

552 homoF[N]homoNal2-[γ-L-Glu]-R-I-D-R-I-NH_2

553 homoF[N]F-[γ-D-Glu]-R-I-D-R-I-NH_2

554 homoF[N]BF-[γ-D-Glu]-R-I-D-R-I-NH_2

555 homoF[N]Nal2-[γ-D-Glu]-R-I-D-R-I-NH_2

556 homoF[N]Nal1-[γ-D-Glu]-R-I-D-R-I-NH_2

557 homoF[N]Cha-[γ-D-Glu]-R-I-D-R-I-NH_2

558 homoF[N]W-[γ-D-Glu]-R-I-D-R-I-NH_2

559 homoF[N]homoF-[γ-D-Glu]-R-I-D-R-I-NH_2

560 homoF[N]homoCha-[γ-D-Glu]-R-I-D-R-I-NH_2

561 homoF[N]homoNal2-[γ-D-Glu]-R-I-D-R-I-NH_2

562 G[N]F-G-G-R-I-D-R-I-NH_2

563 G[N]BF-G-G-R-I-D-R-I-NH_2

564 G[N]Nal2-G-G-R-I-D-R-I-NH_2

565 G[N]Nal1-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

566 G[N]Cha-G-G-R-I-D-R-I-NH_2

567 G[N]W-G-G-R-I-D-R-I-NH_2

568 G[N]homoF-G-G-R-I-D-R-I-NH_2

569 G[N]homoCha-G-G-R-I-D-R-I-NH_2

570 G[N]homoNal2-G-G-R-I-D-R-I-NH_2

571 G[N]F-4-APA-R-I-D-R-I-NH_2

572 G[N]BF-4-APA-R-I-D-R-I-NH_2

573 G[N]Nal2-4-APA-R-I-D-R-I-NH_2

574 G[N]Nal1-4-APA-R-I-D-R-I-NH_2

575 G[N]Cha-4-APA-R-I-D-R-I-NH_2

576 G[N]W-4-APA-R-I-D-R-I-NH_2

577 G[N]homoF-4-APA-R-I-D-R-I-NH_2

578 G[N]homoCha-4-APA-R-I-D-R-I-NH_2

579 G[N]homoNal2-4-APA-R-I-D-R-I-NH_2

580 G[N]F-4-AB-R-I-D-R-I-NH_2

581 G[N]BF-4-AB-R-I-D-R-I-NH_2

582 G[N]Nal2-4-AB-R-I-D-R-I-NH_2

583 G[N]Nal1-4-AB-R-I-D-R-I-NH_2

584 G[N]Cha-4-AB-R-I-D-R-I-NH_2

585 G[N]W-4-AB-R-I-D-R-I-NH_2

586 G[N]homoF-4-AB-R-I-D-R-I-NH_2

587 G[N]homoCha-4-AB-R-I-D-R-I-NH_2

588 G[N]homoNal2-4-AB-R-I-D-R-I-NH_2

589 G[N]F-D-G-R-I-D-R-I-NH_2

590 G[N]BF-D-G-R-I-D-R-I-NH_2

591 G[N]Nal2-D-G-R-I-D-R-I-NH_2

592 G[N]Nal1-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

FIG. 4 (contd.)

593 G[N]Cha-D-G-R-I-D-R-I-NH_2

594 G[N]W-D-G-R-I-D-R-I-NH_2

595 G[N]homoF-D-G-R-I-D-R-I-NH_2

596 G[N]homoCha-D-G-R-I-D-R-I-NH_2

597 G[N]homoNal2-D-G-R-I-D-R-I-NH_2

598 G[N]F-[D-Asp]-G-R-I-D-R-I-NH_2

599 G[N]BF-[D-Asp]-G-R-I-D-R-I-NH_2

600 G[N]Nal2-[D-Asp]-G-R-I-D-R-I-NH_2

601 G[N]Nal1-[D-Asp]-G-R-I-D-R-I-NH_2

602 G[N]Cha-[D-Asp]-G-R-I-D-R-I-NH_2

603 G[N]W-[D-Asp]-G-R-I-D-R-I-NH_2

604 G[N]homoF-[D-Asp]-G-R-I-D-R-I-NH_2

605 G[N]homoCha-[D-Asp]-G-R-I-D-R-I-NH_2

606 G[N]homoNal2-[D-Asp]-G-R-I-D-R-I-NH_2

607 G[N]F-[γ-L-Glu]-R-I-D-R-I-NH_2

608 G[N]BF-[γ-L-Glu]-R-I-D-R-I-NH_2

609 G[N]Nal2-[γ-L-Glu]-R-I-D-R-I-NH_2

610 G[N]Nal1-[γ-L-Glu]-R-I-D-R-I-NH_2

611 G[N]Cha-[γ-L-Glu]-R-I-D-R-I-NH_2

612 G[N]W-[γ-L-Glu]-R-I-D-R-I-NH_2

613 G[N]homoF-[γ-L-Glu]-R-I-D-R-I-NH_2

614 G[N]homoCha-[γ-L-Glu]-R-I-D-R-I-NH_2

615 G[N]homoNal2-[γ-L-Glu]-R-I-D-R-I-NH_2

616 G[N]F-[γ-D-Glu]-R-I-D-R-I-NH_2

617 G[N]BF-[γ-D-Glu]-R-I-D-R-I-NH_2

618 G[N]Nal2-[γ-D-Glu]-R-I-D-R-I-NH_2

619 G[N]Nal1-[γ-D-Glu]-R-I-D-R-I-NH_2

620 G[N]Cha-[γ-D-Glu]-R-I-D-R-I-NH_2

621 G[N]W-[γ-D-Glu]-R-I-D-R-I-NH_2

622 G[N]homoF-[γ-D-Glu]-R-I-D-R-I-NH_2

623 G[N]homoCha-[γ-D-Glu]-R-I-D-R-I-NH_2

624 G[N]homoNal2-[γ-D-Glu]-R-I-D-R-I-NH_2

625 BMAL-G-G-R-I-D-R-I-NH_2

626 PBMAL-G-G-R-I-D-R-I-NH_2

627 NMAL2-G-G-R-I-D-R-I-NH_2

628 NMAL1-G-G-R-I-D-R-I-NH_2

629 CMAL-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

630 PMAL-G-G-R-I-D-R-I-NH_2

631 NOMAL2-G-G-R-I-D-R-I-NH_2

632 IMAL-G-G-R-I-D-R-I-NH_2

633 PEMAL-G-G-R-I-D-R-I-NH_2

634 CEMAL-G-G-R-I-D-R-I-NH_2

635 NEMAL-G-G-R-I-D-R-I-NH_2

636 BMAL-4-APA-R-I-D-R-I-NH_2

637 PBMAL-4-APA-R-I-D-R-I-NH_2

638 NMAL2-4-APA-R-I-D-R-I-NH_2

639 NMAL1-4-APA-R-I-D-R-I-NH_2

640 CMAL-4-APA-R-I-D-R-I-NH_2

641 PMAL-4-APA-R-I-D-R-I-NH_2

642 NOMAL2-4-APA-R-I-D-R-I-NH_2

643 IMAL-4-APA-R-I-D-R-I-NH_2

644 PEMAL-4-APA-R-I-D-R-I-NH_2

645 CEMAL-4-APA-R-I-D-R-I-NH_2

646 NEMAL-4-APA-R-I-D-R-I-NH_2

647 BMAL-4-AB-R-I-D-R-I-NH_2

648 PBMAL-4-AB-R-I-D-R-I-NH_2

649 NMAL2-4-AB-R-I-D-R-I-NH_2

650 NMAL1-4-AB-R-I-D-R-I-NH_2

651 CMAL-4-AB-R-I-D-R-I-NH_2

652 PMAL-4-AB-R-I-D-R-I-NH_2

653 NOMAL2-4-AB-R-I-D-R-I-NH_2

654 IMAL-4-AB-R-I-D-R-I-NH_2

655 PEMAL-4-AB-R-I-D-R-I-NH_2

656 CEMAL-4-AB-R-I-D-R-I-NH_2

657 NEMAL-4-AB-R-I-D-R-I-NH_2

658 BMAL-D-G-R-I-D-R-I-NH_2

659 PBMAL-D-G-R-I-D-R-I-NH_2

660 NMAL2-D-G-R-I-D-R-I-NH_2

661 NMAL1-D-G-R-I-D-R-I-NH_2

662 CMAL-D-G-R-I-D-R-I-NH_2

663 PMAL-D-G-R-I-D-R-I-NH_2

664 NOMAL2-D-G-R-I-D-R-I-NH_2

665 IMAL-D-G-R-I-D-R-I-NH_2

666 PEMAL-D-G-R-I-D-R-I-NH_2

667 CEMAL-D-G-R-I-D-R-I-NH_2

668 NEMAL-D-G-R-I-D-R-I-NH_2

669 BMAL-[D-Asp]-G-R-I-D-R-I-NH_2

670 PBMAL-[D-Asp]-G-R-I-D-R-I-NH_2

671 NMAL2-[D-Asp]-G-R-I-D-R-I-NH_2

672 NMAL1-[D-Asp]-G-R-I-D-R-I-NH_2

673 CMAL-[D-Asp]-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

674 PMAL-[D-Asp]-G-R-I-D-R-I-NH_2

675 NOMAL2-[D-Asp]-G-R-I-D-R-I-NH_2

676 IMAL-[D-Asp]-G-R-I-D-R-I-NH_2

677 PEMAL-[D-Asp]-G-R-I-D-R-I-NH_2

678 CEMAL-[D-Asp]-G-R-I-D-R-I-NH_2

679 NEMAL-[D-Asp]-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

680 BMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

681 PBMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

682 NMAL2-[γ-L-Glu]-R-I-D-R-I-NH_2

683 NMAL1-[γ-L-Glu]-R-I-D-R-I-NH_2

684 CMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

685 PMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

686 NOMAL2-[γ-L-Glu]-R-I-D-R-I-NH_2

687 IMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

688 PEMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

589 CEMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

690 NEMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

691 BMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

692 PBMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

693 NMAL2-[γ-D-Glu]-R-I-D-R-I-NH_2

694 NMAL1-[γ-D-Glu]-R-I-D-R-I-NH_2

695 CMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

696 PMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

697 NOMAL2-[γ-D-Glu]-R-I-D-R-I-NH_2

698 IMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

699 PEMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

700 CEMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

701 NEMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

702 HAF[N]G-G-R-I-D-R-I-NH_2

703 HABF[N]G-G-R-I-D-R-I-NH_2

704 HANal2[N]G-G-R-I-D-R-I-NH_2

705 HANal1[N]G-G-R-I-D-R-I-NH_2

706 HACha[N]G-G-R-I-D-R-I-NH_2

707 HAW[N]G-G-R-I-D-R-I-NH_2

708 HAhomoF[N]G-G-R-I-D-R-I-NH_2

709 HAhomoCha[N]G-G-R-I-D-R-I-NH_2

710 HAhomoNal2[N]G-G-R-I-D-R-I-NH_2

711 HAF[N]4-APA-R-I-D-R-I-NH_2

712 HABF[N]4-APA-R-I-D-R-I-NH_2

713 HANal2[N]4-APA-R-I-D-R-I-NH_2

714 NANal1[N]4-APA-R-I-D-R-I-NH_2

715 HACha[N]4-APA-R-I-D-R-I-NH_2

716 HAW[N]4-APA-R-I-D-R-I-NH_2

717 HAhomoF[N]4-APA-R-I-D-R-I-NH_2

718 HAhomoCha[N]4-APA-R-I-D-R-I-NH_2

719 HAhomoNal2[N]4-APA-R-I-D-R-I-NH_2

720 HAF[N]4-AB-R-I-D-R-I-NH_2

721 HABF[N]4-AB-R-I-D-R-I-NH_2

722 HANal2[N]4-AB-R-I-D-R-I-NH_2

723 HANal1[N]4-AB-R-I-D-R-I-NH_2

724 HACha[N]4-AB-R-I-D-R-I-NH_2

725 HAW[N]4-AB-R-I-D-R-I-NH_2

726 HAhomoF[N]4-AB-R-I-D-R-I-NH_2

727 HAhomoCha[N]4-AB-R-I-D-R-I-NH_2

FIG. 4 (contd.)

728 HAhomoNal2[N]4-AB-R-I-D-R-I-NH_2

729 HAF[N]D-G-R-I-D-R-I-NH_2

730 HABF[N]D-G-R-I-D-R-I-NH_2

731 HANal2[N]D-G-R-I-D-R-I-NH_2

732 HANal1[N]D-G-R-I-D-R-I-NH_2

733 HACha[N]D-G-R-I-D-R-I-NH_2

734 HAW[N]D-G-R-I-D-R-I-NH_2

735 HAhomoF[N]D-G-R-I-D-R-I-NH_2

736 HAhomoCha[N]D-G-R-I-D-R-I-NH_2

737 HAhomoNal2[N]D-G-R-I-D-R-I-NH_2

738 HAF[N][D-Asp]-G-R-I-D-R-I-NH_2

739 HABF[N][D-Asp]-G-R-I-D-R-I-NH_2

740 HANal2[N][D-Asp]-G-R-I-D-R-I-NH_2

741 HANal1[N][D-Asp]-G-R-I-D-R-I-NH_2

742 HACha[N][D-Asp]-G-R-I-D-R-I-NH_2

743 HAW[N][D-Asp]-G-R-I-D-R-I-NH_2

744 HAhomoF[N][D-Asp]-G-R-I-D-R-I-NH_2

745 HAhomoCha[N][D-Asp]-G-R-I-D-R-I-NH_2

746 HAhomoNal2[N][D-Asp]-G-R-I-D-R-I-NH_2

747 HAF[N][γ-L-Glu]-R-I-D-R-I-NH_2

748 HABF[N][γ-L-Glu]-R-I-D-R-I-NH_2

749 HANal2[N][γ-L-Glu]-R-I-D-R-I-NH_2

750 NANal1[N][γ-L-Glu]-R-I-D-R-I-NH_2

751 HACha[N][γ-L-Glu]-R-I-D-R-I-NH_2

752 HAW[N][γ-L-Glu]-R-I-D-R-I-NH_2

753 HAhomoF[N][γ-L-Glu]-R-I-D-R-I-NH_2

754 HAhomoCha[N][γ-L-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

755 HAhomoNal2[N][γ-L-Glu]-R-I-D-R-I-NH_2

756 HAF[N]{γ-D-Glu]-R-I-D-R-I-NH_2

757 HABF[N][γ-D-Glu]-R-I-D-R-I-NH_2

758 HANal2[N][γ-D-Glu]-R-I-D-R-I-NH_2

759 HANal1[N][γ-D-Glu]-R-I-D-R-I-NH_2

760 HACha[N][γ-D-Glu]-R-I-D-R-I-NH_2

761 HAW[N][γ-D-Glu]-R-I-D-R-I-NH_2

762 HAhomoF[N][γ-D-Glu]-R-I-D-R-I-NH_2

763 HAhomoCha[N][γ-D-Glu]-R-I-D-R-I-NH_2

764 HAhomoNal2[N][γ-D-Glu]-R-I-D-R-I-NH_2

765 BHAMAL-G-G-R-I-D-R-I-NH_2

766 PBHAMAL-G-G-R-I-D-R-I-NH_2

767 NHAMAL2-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

768 NHAMAL1-G-G-R-I-D-R-I-NH_2

769 CHAMAL-G-G-R-I-D-R-I-NH_2

770 PHAMAL-G-G-R-I-D-R-I-NH_2

771 NOHAMAL2-G-G-R-I-D-R-I-NH_2

772 IHAMAL-G-G-R-I-D-R-I-NH_2

773 PEHAMAL-G-G-R-I-D-R-I-NH_2

774 CEHAMAL-G-G-R-I-D-R-I-NH_2

775 NEHAMAL-G-G-R-I-D-R-I-NH_2

776 BHAMAL-4-APA-R-I-D-R-I-NH_2

777 PBHAMAL-4-APA-R-I-D-R-I-NH_2

778 NHAMAL2-4-APA-R-I-D-R-I-NH_2

779 NHAMAL1-4-APA-R-I-D-R-I-NH_2

780 CHAMAL-4-APA-R-I-D-R-I-NH_2

781 PHAMAL-4-APA-R-I-D-R-I-NH_2

782 NOHAMAL2-4-APA-R-I-D-R-I-NH_2

783 IHAMAL-4-APA-R-I-D-R-I-NH_2

784 PEHAMAL-4-APA-R-I-D-R-I-NH_2

785 CEHAMAL-4-APA-R-I-D-R-I-NH_2

786 NEHAMAL-4-APA-R-I-D-R-I-NH_2

787 BHAMAL-4-AB-R-I-D-R-I-NH_2

788 PBHAMAL-4-AB-R-I-D-R-I-NH_2

789 NHAMAL2-4-AB-R-I-D-R-I-NH_2

790 NHAMAL1-4-AB-R-I-D-R-I-NH_2

791 CHAMAL-4-AB-R-I-D-R-I-NH_2

792 PHAMAL-4-AB-R-I-D-R-I-NH_2

793 NOHAMAL2-4-AB-R-I-D-R-I-NH_2

794 IHAMAL-4-AB-R-I-D-R-I-NH_2

795 PEHAMAL-4-AB-R-I-D-R-I-NH_2

796 CEHAMAL-4-AB-R-I-D-R-I-NH_2

797 NEHAMAL-4-AB-R-I-D-R-I-NH_2

798 BHAMAL-D-G-R-I-D-R-I-NH_2

799 PBHAMAL-D-G-R-I-D-R-I-NH_2

800 NHAMAL2-D-G-R-I-D-R-I-NH_2

801 NHAMAL1-D-G-R-I-D-R-I-NH_2

802 CHAMAL-D-G-R-I-D-R-I-NH_2

803 PHAMAL-D-G-R-I-D-R-I-NH_2

804 NOHAMAL2-D-G-R-I-D-R-I-NH_2

805 IHAMAL-D-G-R-I-D-R-I-NH_2

806 PEHAMAL-D-G-R-I-D-R-I-NH_2

807 CEHAMAL-D-G-R-I-D-R-I-NH_2

808 NEHAMAL-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

809 BHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

810 PBHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

811 NHAMAL2-[D-Asp]-G-R-I-D-R-I-NH_2

812 NHAMAL1-[D-Asp]-G-R-I-D-R-I-NH_2

813 CHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

814 PHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

815 NOHAMAL2-[D-Asp]-G-R-I-D-R-I-NH_2

816 IHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

817 PEHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

818 CEHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

819 NEHAMAL-[D-Asp]-G-R-I-D-R-I-NH_2

820 BHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

821 PBHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

822 NHAMAL2-[γ-L-Glu]-R-I-D-R-I-NH_2

823 NHAMAL1-[γ-L-Glu]-R-I-D-R-I-NH_2

824 CHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

825 PHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

826 NOHAMAL2-[γ-L-Glu]-R-I-D-R-I-NH_2

827 IHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

828 PEHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

829 CEHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

830 NEHAMAL-[γ-L-Glu]-R-I-D-R-I-NH_2

831 BHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

832 PBHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

833 NHAMAL2-[γ-D-Glu]-R-I-D-R-I-NH_2

834 NHAMAL1-[γ-D-Glu]-R-I-D-R-I-NH_2

835 CHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

836 PHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

837 NOHAMAL2-[γ-D-Glu]-R-I-D-R-I-NH_2

838 IHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

839 PEHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

840 CEHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

841 NEHAMAL-[γ-D-Glu]-R-I-D-R-I-NH_2

842 BHASUC-G-G-R-I-D-R-I-NH_2

843 PBHASUC-G-G-R-I-D-R-I-NH_2

844 NHASUC2-G-G-R-I-D-R-I-NH_2

845 NHASUC1-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

846 CHASUC-G-G-R-I-D-R-I-NH_2

847 PHASUC-G-G-R-I-D-R-I-NH_2

848 NOHASUC2-G-G-R-I-D-R-I-NH_2

849 IHASUC-G-G-R-I-D-R-I-NH_2

850 PEHASUC-G-G-R-I-D-R-I-NH_2

851 CEHASUC-G-G-R-I-D-R-I-NH_2

852 NEHASUC-G-G-R-I-D-R-I-NH_2

853 BHASUC-4-APA-R-I-D-R-I-NH_2

854 PBHASUC-4-APA-R-I-D-R-I-NH_2

855 NHASUC2-4-APA-R-I-D-R-I-NH_2

856 NHASUC1-4-APA-R-I-D-R-I-NH_2

857 CHASUC-4-APA-R-I-D-R-I-NH_2

858 PHASUC-4-APA-R-I-D-R-I-NH_2

859 NOHASUC2-4-APA-R-I-D-R-I-NH_2

860 IHASUC-4-APA-R-I-D-R-I-NH_2

861 PEHASUC-4-APA-R-I-D-R-I-NH_2

862 CEHASUC-4-APA-R-I-D-R-I-NH_2

863 NEHASUC-4-APA-R-I-D-R-I-NH_2

864 BHASUC-4-AB-R-I-D-R-I-NH_2

865 PBHASUC-4-AB-R-I-D-R-I-NH_2

866 NHASUC2-4-AB-R-I-D-R-I-NH_2

867 NHASUC1-4-AB-R-I-D-R-I-NH_2

868 CHASUC-4-AB-R-I-D-R-I-NH_2

869 PHASUC-4-AB-R-I-D-R-I-NH_2

870 NOHASUC2-4-AB-R-I-D-R-I-NH_2

871 IHASUC-4-AB-R-I-D-R-I-NH_2

872 PEHASUC-4-AB-R-I-D-R-I-NH_2

873 CEHASUC-4-AB-R-I-D-R-I-NH_2

874 NEHASUC-4-AB-R-I-D-R-I-NH_2

875 BHASUC-D-G-R-I-D-R-I-NH_2

876 PBHASUC-D-G-R-I-D-R-I-NH_2

877 NHASUC2-D-G-R-I-D-R-I-NH_2

878 NHASUC1-D-G-R-I-D-R-I-NH_2

879 CHASUC-D-G-R-I-D-R-I-NH_2

880 PHASUC-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

881 NOHASUC2-D-G-R-I-D-R-I-NH_2

882 IHASUC-D-G-R-I-D-R-I-NH_2

883 PEHASUC-D-G-R-I-D-R-I-NH_2

884 CEHASUC-D-G-R-I-D-R-I-NH_2

885 NEHASUC-D-G-R-I-D-R-I-NH_2

886 BHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

887 PBHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

888 NHASUC2-[D-Asp]-G-R-I-D-R-I-NH_2

889 NHASUC1-[D-Asp]-G-R-I-D-R-I-NH_2

890 CHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

891 PHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

892 NOHASUC2-[D-Asp]-G-R-I-D-R-I-NH_2

893 IHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

894 PEHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

895 CEHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

896 NEHASUC-[D-Asp]-G-R-I-D-R-I-NH_2

897 BHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

898 PBHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

899 NHASUC2-[γ-L-Glu]-R-I-D-R-I-NH_2

900 NHASUC1-[γ-L-Glu]-R-I-D-R-I-NH_2

901 CHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

902 PHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

903 NOHASUC2-[γ-L-Glu]-R-I-D-R-I-NH_2

904 IHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

905 PEHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

906 CEHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

907 NEHASUC-[γ-L-Glu]-R-I-D-R-I-NH_2

908 BHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

909 PBHASUC-[γ-D-Glu]-R-I-D-R I-NH_2

910 NHASUC2-[γ-D-Glu]-R-I-D-R-I-NH_2

911 NHASUC1-[γ-D-Glu]-R-I-D-R-I-NH_2

912 CHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

913 PHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

914 NOHASUC2-[γ-D-Glu]-R-I-D-R-I-NH_2

915 IHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

916 PEHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

917 CEHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

918 NEHASUC-[γ-D-Glu]-R-I-D-R-I-NH_2

919 Phosphoryl-F-G-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

920 Phosphoryl-BF-G-G-R-I-D-R-I-NH_2

921 Phosphoryl-Nal2-G-G-R-I-D-R-I-NH_2

922 Phosphoryl-Nal1-G-G-R-I-D-R-I-NH_2

923 Phosphoryl-Cha-G-G-R-I-D-R-I-NH_2

924 Phosphoryl-W-G-G-R-I-D-R-I-NH_2

925 Phosphoryl-homoF-G-G-R-I-D-R-I-NH_2

926 Phosphoryl-homoCha-G-G-R-I-D-R-I-NH_2

927 Phosphoryl-homoNal2-G-G-R-I-D-R-I-NH_2

928 Phosphoryl-F-4-APA-R-I-D-R-I-NH_2

929 Phosphoryl-BF-4-APA-R-I-D-R-I-NH_2

930 Phosphoryl-Nal2-4-APA-R-I-D-R-I-NH_2

931 Phosphoryl-Nal1-4-APA-R-I-D-R-I-NH_2

932 Phosphoryl-Cha-4-APA-R-I-D-R-I-NH_2

933 Phosphoryl-W-4-APA-R-I-D-R-I-NH_2

934 Phosphoryl-homoF-4-APA-R-I-D-R-I-NH_2

935 Phosphoryl-homoCha-4-APA-R-I-D-R-I-NH_2

936 Phosphoryl-homoNal2-4-APA-R-I-D-R-I-NH_2

937 Phosphoryl-F-4-AB-R-I-D-R-I-NH_2

938 Phosphoryl-BF-4-AB-R-I-D-R-I-NH_2

939 Phosphoryl-Nal2-4-AB-R-I-D-R-I-NH_2

940 Phosphoryl-Nal2-4-AB-R-I-D-R-I-NH_2

941 Phosphoryl-Cha-4-AB-R-I-D-R-I-NH_2

942 Phosphoryl-W-4-AB-R-I-D-R-I-NH_2

943 Phosphoryl-homoF-4-AB-R-I-D-R-I-NH_2

944 Phosphoryl-homoCha-4-AB-R-I-D-R-I-NH_2

945 Phosphoryl-homoNal2-4-AB-R-I-D-R-I-NH_2

946 Phosphoryl-F-D-G-R-I-D-R-I-NH_2

947 Phosphoryl-BF-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

948 Phosphoryl-Nal2-D-G-R-I-D-R-I-NH_2

949 Phosphoryl-Nal1-D-G-R-I-D-R-I-NH_2

950 Phosphoryl-Cha-D-G-R-I-D-R-I-NH_2

951 Phosphoryl-W-D-G-R-I-D-R-I-NH_2

952 Phosphoryl-homoF-D-G-R-I-D-R-I-NH_2

953 Phosphoryl-homoCha-D-G-R-I-D-R-I-NH_2

954 Phosphoryl-homoNal2-D-G-R-I-D-R-I-NH_2

955 Phosphoryl-F-[D-Asp]-G-R-I-D-R-I-NH_2

956 Phosphoryl-BF-[D-Asp]-G-R-I-D-R-I-NH_2

957 Phosphoryl-Nal2-[D-Asp]-G-R-I-D-R-I-NH_2

958 Phosphoryl-Nal1-[D-Asp]-G-R-I-D-R-I-NH_2

959 Phosphoryl-Cha-[D-Asp]-G-R-I-D-R-I-NH_2

960 Phosphoryl-W-[D-Asp]-G-R-I-D-R-I-NH_2

961 Phosphoryl-homoF-[D-Asp]-G-R-I-D-R-I-NH_2

962 Phosphoryl-homoCha-[D-Asp]-G-R-I-D-R-I-NH_2

963 Phosphoryl-homoNal2-[D-Asp]-G-R-I-D-R-I-NH_2

964 Phosphoryl-F-[γ-L-Glu]-R-I-D-R-I-NH_2

965 Phosphoryl-BF-[γ-L-Glu]-R-I-D-R-I-NH_2

966 Phosphoryl-Nal2-[γ-L-Glu]-R-I-D-R-I-NH_2

967 Phosphoryl-Nal1-[γ-L-Glu]-R-I-D-R-I-NH_2

968 Phosphoryl-Cha-[γ-L-Glu]-R-I-D-R-I-NH_2

969 Phosphoryl-W-[γ-L-Glu]-R-I-D-R-I-NH_2

970 Phosphoryl-homoF-[γ-L-Glu]-R-I-D-R-I-NH_2

971 Phosphoryl-homoCha-[γ-L-Glu]-R-I-D-R-I-NH_2

972 Phosphoryl-homoNal2-[γ-L-Glu]-R-I-D-R-I-NH_2

973 Phosphoryl-F-[γ-D-Glu]-R-I-D-R-I-NH_2

974 Phosphoryl-BF-[γ-D-Glu]-R-I-D-R-I-NH_2

975 Phosphoryl-Nal2-[γ-D-Glu]-R-I-D-R-I-NH_2

976 Phosphoryl-Nal1-[γ-D-Glu]-R-I-D-R-I-NH_2

977 Phosphoryl-Cha-[γ-D-Glu]-R-I-D-R-I-NH_2

978 Phosphoryl-W-[γ-D-Glu]-R-I-D-R-I-NH_2

979 Phosphoryl-homoF-[γ-D-Glu]-R-I-D-R-I-NH_2

980 Phosphoryl-homoCha-[γ-D-Glu]-R-I-D-R-I-NH_2

981 Phosphoryl-homoNal2-[γ-D-Glu]-R-I-D-R-I-NH_2

982 BSUC-G-G-R-I-D-R-I-NH_2

983 PBSUC-G-G-R-I-D-R-I-NH_2

984 NSUC2-G-G-R-I-D-R-I-NH_2

985 NSUC1-G-G-R-I-D-R-I-NH_2

986 CSUC-G-G-R-I-D-R-I-NH_2

987 PSUC-G-G-R-I-D-R-I-NH_2

988 ISUC-G-G-R-I-D-R-I-NH_2

989 PESUC-G-G-R-I-D-R-I-NH_2

990 NESUC-G-G-R-I-D-R-I-NH_2

991 BSUC-4-APA-R-I-D-R-I-NH_2

992 PBSUC-4-APA-R-I-D-R-I-NH_2

993 NSUC2-4-APA-R-I-D-R-I-NH_2

994 NSUC1-4-APA-R-I-D-R-I-NH_2

995 CSUC-4-APA-R-I-D-R-I-NH_2

996 PSUC-4-APA-R-I-D-R-I-NH_2

997 NOSUC2-4-APA-R-I-D-R-I-NH_2

FIG. 4 (contd.)

998 ISUC-4-APA-R-I-D-R-I-NH_2

999 PESUC-4-APA-R-I-D-R-I-NH_2

1000 CESUC-4-APA-R-I-D-R-I-NH_2

1001 NESUC-4-APA-R-I-D-R-I-NH_2

1002 BSUC-4-AB-R-I-D-R-I-NH_2

1003 PBSUC-4-AB-R-I-D-R-I-NH_2

1004 NSUC2-4-AB-R-I-D-R-I-NH_2

1005 NSUC1-4-AB-R-I-D-R-I-NH_2

1006 CSUC-4-AB-R-I-D-R-I-NH_2

1007 PSUC-4-AB-R-I-D-R-I-NH_2

1008 NOSUC2-4-AB-R-I-D-R-I-NH_2

1009 ISUC-4-AB-R-I-D-R-I-NH_2

1010 PESUC-4-AB-R-I-D-R-I-NH_2

1011 CESUC-4-AB-R-I-D-R-I-NH_2

1012 NESUC-4-AB-R-I-D-R-I-NH_2

1013 BSUC-D-G-R-I-D-R-I-NH_2

1014 PBSUC-D-G-R-I-D-R-I-NH_2

FIG. 4 (contd.)

1015 NSUC2-D-G-R-I-D-R-I-NH_2

1016 NSUC1-D-G-R-I-D-R-I-NH_2

1017 CSUC-D-G-R-I-D-R-I-NH_2

1018 PSUC-D-G-R-I-D-R-I-NH_2

1019 NOSUC2-D-G-R-I-D-R-I-NH_2

1020 ISUC-D-G-R-I-D-R-I-NH_2

1021 PESUC-D-G-R-I-D-R-I-NH_2

1022 CESUC-D-G-R-I-D-R-I-NH_2

1023 NESUC-D-G-R-I-D-R-I-NH_2

1024 BSUC-[D-Asp]-G-R-I-D-R-I-NH_2

1025 PBSUC-[D-Asp]-G-R-I-D-R-I-NH_2

1026 NSUC2-[D-Asp]-G-R-I-D-R-I-NH_2

1027 NSUC1-[D-Asp]-G-R-I-D-R-I-NH_2

1028 CSUC-[D-Asp]-G-R-I-D-R-I-NH_2

1029 PSUC-[D-Asp]-G-R-I-D-R-I-NH_2

1030 NOSUC2-[D-Asp]-G-R-I-D-R-I-NH_2

1031 ISUC-[D-Asp]-G-R-I-D-R-I-NH_2

1032 PESUC-[D-Asp]-G-R-I-D-R-I-NH_2

1033 CESUC-[D-Asp]-G-R-I-D-R-I-NH_2

1034 NESUC-[D-Asp]-G-R-I-D-R-I-NH_2

1035 BSUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1036 PBSUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1037 NSUC2-[γ-L-Glu]-R-I-D-R-I-NH_2

1038 NSUC1-[γ-L-Glu]-R-I-D-R-I-NH_2

1039 CSUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1040 PSUC-[γ-L-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

1041 NOSUC2-[γ-L-Glu]-R-I-D-R-I-NH_2

1042 ISUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1043 PESUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1044 CESUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1045 NESUC-[γ-L-Glu]-R-I-D-R-I-NH_2

1046 BSUC-[γ-D-Glu]-R-I-D-R-I-NH_2

1047 PBSUC-[γ-D-Glu]-R-I-D-R-I-NH_2

1048 NSUC2-[γ-D-Glu]-R-I-D-R-I-NH_2

1049 NSUC1-[γ-D-Glu]-R-I-D-R-I-NH_2

1050 CSUC-[γ-D-Glu]-R-I-D-R-I-NH_2

1051 PSUC-[γ-D-Glu]-R-I-D-R-I-NH_2

FIG. 4 (contd.)

1052	NOSUC2-[γ-D-Glu]-R-I-D-R-I-NH_2
1053	ISUC-[γ-D-Glu]-R-I-D-R-I-NH_2
1054	PESUC-[γ-D-Glu]-R-I-D-R-I-NH_2
1055	CESUC-[γ-D-Glu]-R-I-D-R-I-NH_2
1056	NESUC-[γ-D-Glu]-R-I-D-R-I-NH_2

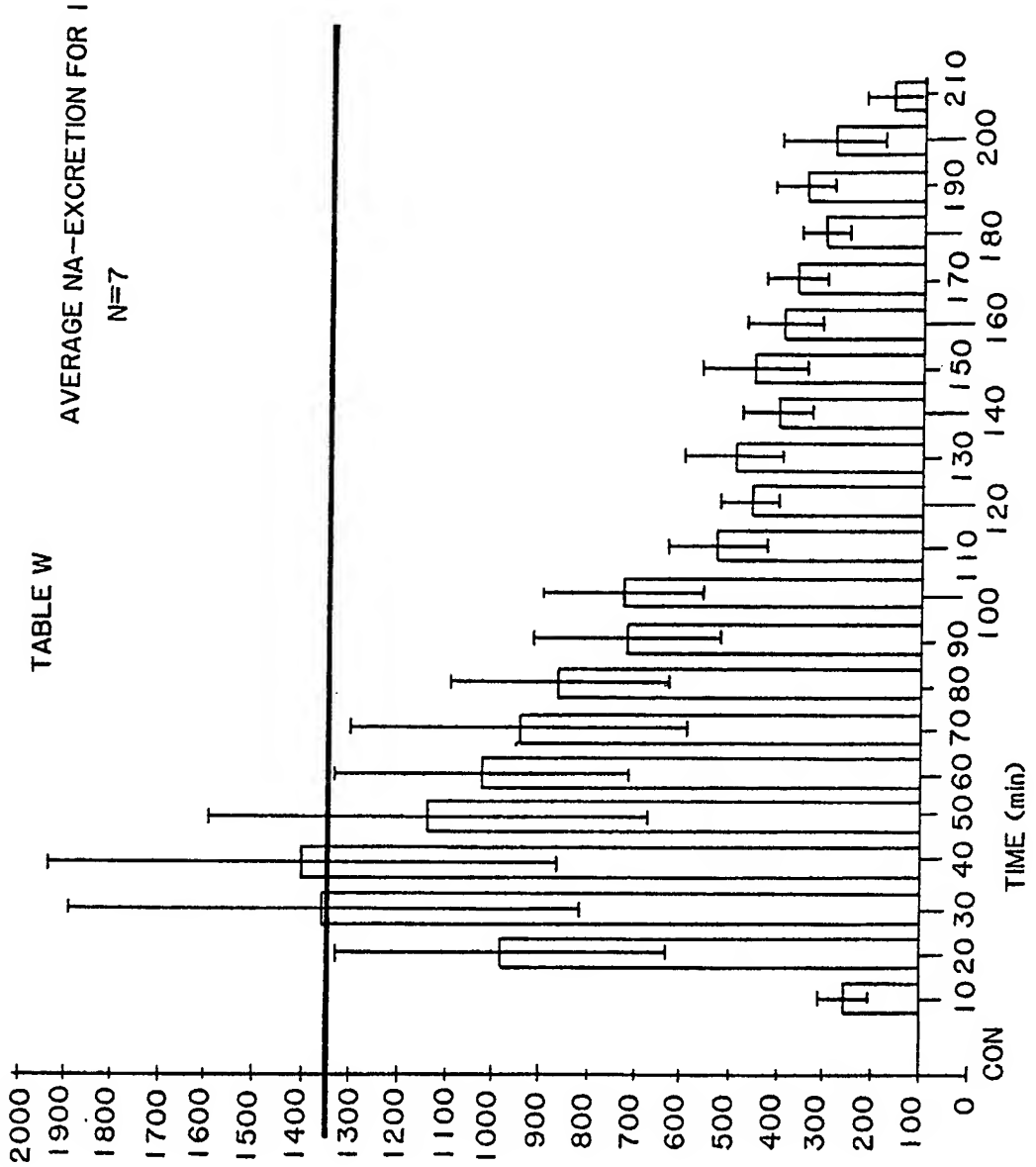


TABLE W
AVERAGE NA-EXCRETION FOR I
N=7
NA_EX2AVE
A-EXCRETION
(% OF CONTROL)
TIME (min)
CON
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

FIG.5A

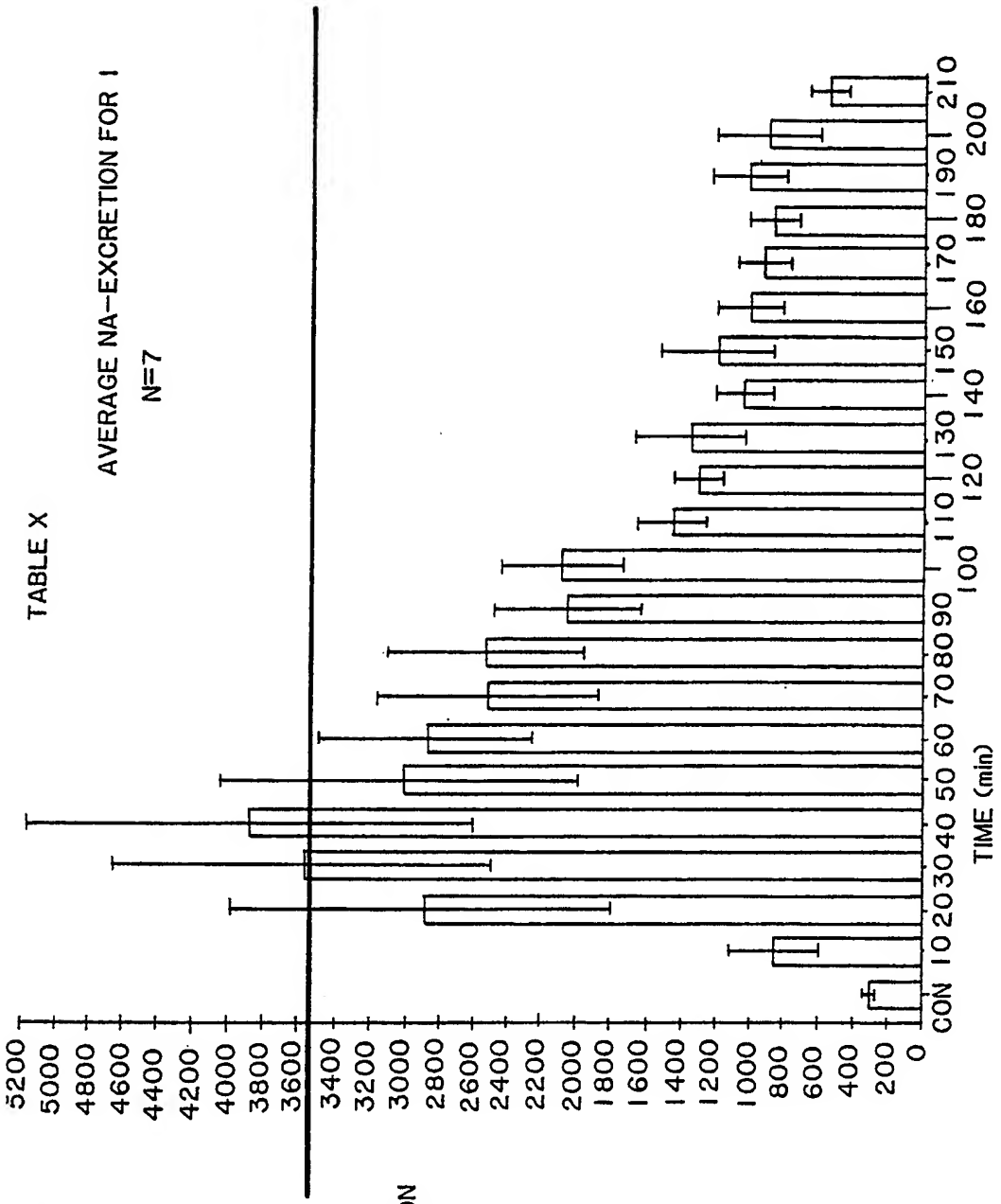


TABLE X
AVERAGE NA-EXCRETION FOR 1
N=7
NA_EX_AVE3
NA-EXCRETION
(neg/min)
TIME (min)
CON 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000 3200 3400 3600 3800 4000 4200 4400 4600 4800 5000 5200

FIG.5B

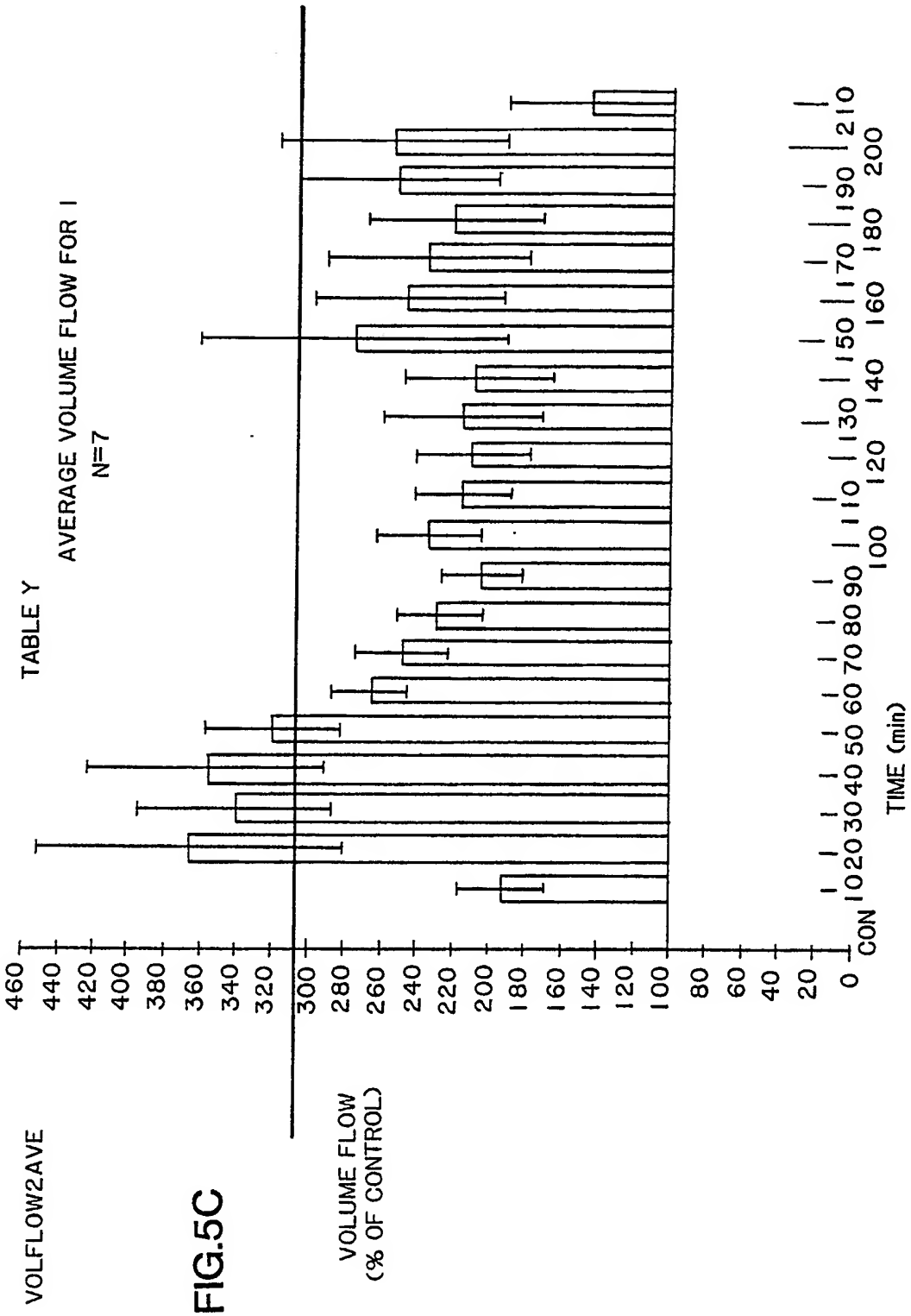


TABLE Y
AVERAGE VOLUME FLOW FOR I
N=7
VOLFLOW2AVE
VOLUME FLOW
(% OF CONTROL)
460
440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
CON 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
TIME (min)

FIG.5C

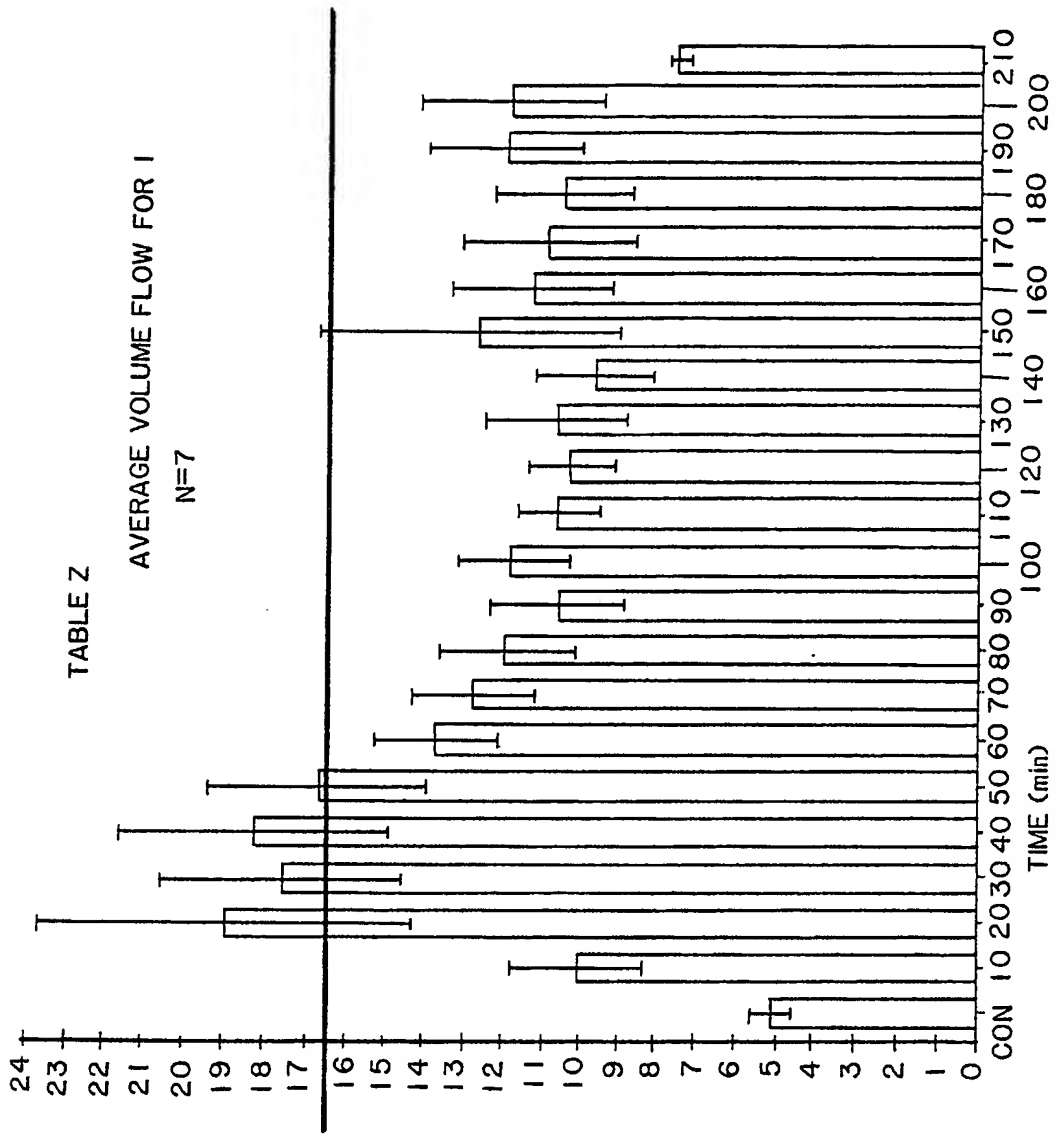


TABLE Z
AVERAGE VOLUME FLOW FOR I
N=7
VOLAVE3
VOLUME FLOW (ul/min)
TIME (min)
CON 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

FIG.5D

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/03466

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61 K 37/02, C07K 7/06 C07K 7/08, C07K 7/10, C07K 1/06

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	530/324,530/535,530/326, 530/327,530/328

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y,P	U.S., A, 4,804,650, Lewicki, Published 14 February, 1989.	1-16
Y	U.S., A, 4,740,499, Olins, Published 26 April 1988.	1-16
Y	U.S., A, 4,513,009, Roques, Published 23 April 1985	1-16
Y	U.S., A 4,749,688 Haslanger Published 7 June 1988.	1-16
Y	EP, B 0254032, Haslanger, Published 27 January 1988.	1-16

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

29 November 1989

Date of Mailing of this International Search Report

18 DEC 1989

International Searching Authority

ISA/US

Signature of Authorized Officer

Susan M. Perkins

Susan M. Perkins

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Fennell, FASEB Journal, 2: A936, Published 1988	1-16
Y	Seymour, FASEB Journal, 2: A936, Published 1988.	1-16
Y	Trapani, FASEB Journal, 2: A936, Published 1988.	1-16
Y	McMartin, FASEB Journal, 2: A936, Published 1988.	1-16
Y	Stephenson, Biochemical Journal, 243: 183-187, Published 1987.	1-16
Y	Koepke, FASEB Journal 2: A527, Published 1988.	1-16